BENZAZEPINE DERIVATIVES FOR THE TREATMENT OF NEUROLOGICAL AND PSYCHIATRIC DISORDERS

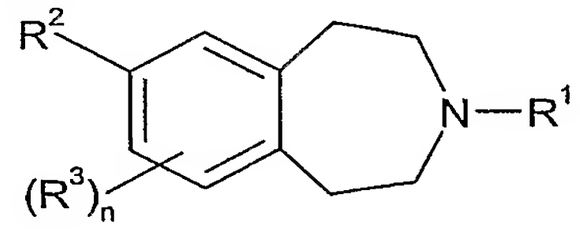
The present invention relates to novel benzazepine derivatives having pharmacological activity, processes for their preparation, to compositions containing them and to their use in the treatment of neurological and psychiatric disorders.

JP 2001226269 and WO 00/23437 (Takeda Chem Ind Ltd) describe a series of benzazepine derivatives which are claimed to be useful in the treatment of obesity. DE 2207430, US 4,210,749 and FR 2171879 (Pennwalt Corp) and GB 1268243 (Wallace and Tiernan Inc) all describe a series of benzazepine derivatives which are claimed as being antagonists for narcotics (such as morphine or codeine) and also anti-histamines and anticholinergic agents. WO 02/14513 (Takeda Chem Ind Ltd) describe a series of benzazepine derivatives with GPR12 activity which are claimed to be useful in the treatment of attention deficit disorder, narcolepsy or anxiety. WO 02/02530 (Takeda Chem Ind Ltd) describe a series of benzazepine derivatives as GPR14 antagonists which are claimed to be useful in the treatment of hypertension, atherosclerosis and cardiac infarction. WO 01/03680 (Isis Innovation Ltd) describe a series of benzazepine derivatives which are claimed as effective agents in the preparation of cells for transplantation in addition to the inhibition of diseases such as diabetes. WO 00/21951 (SmithKline Beecham plc) discloses a series of tetrahydrobenzazepine derivatives as modulators of dopamine D3 receptors which are claimed to be useful as antipsychotic agents. WO 01/87834 (Takeda Chem Ind Ltd) describe a series of benzazepine derivatives as MCH antagonists which are claimed to be useful in the treatment of obesity. WO 02/15934 (Takeda Chem Ind Ltd) describe a series of benzazepine derivatives as urotensin II receptor antagonists which are claimed to be useful in the treatment of neurodegenerative disorders. WO 04/018432 (Eli Lilly and Company) describe a series of substituted azepines as histamine H3 receptor antagonists.

The histamine H3 receptor is predominantly expressed in the mammalian central nervous system (CNS), with minimal expression in peripheral tissues except on some sympathetic nerves (Leurs *et al.*, (1998), Trends Pharmacol. Sci. **19**, 177-183). Activation of H3 receptors by selective agonists or histamine results in the inhibition of neurotransmitter release from a variety of different nerve populations, including histaminergic and cholinergic neurons (Schlicker *et al.*, (1994), Fundam. Clin. Pharmacol. **8**, 128-137). Additionally, *in vitro* and *in vivo* studies have shown that H3 antagonists can facilitate neurotransmitter release in brain areas such as the cerebral cortex and hippocampus, relevant to cognition (Onodera *et al.*, (1998), In: The Histamine H3 receptor, ed Leurs and Timmerman, pp255-267, Elsevier Science B.V.). Moreover, a number of reports in the literature have demonstrated the cognitive enhancing properties of H3 antagonists (e.g. thioperamide, clobenpropit, ciproxifan and GT-2331) in rodent models including the five choice task, object recognition, elevated plus maze, acquisition of novel task and passive avoidance (Giovanni *et al.*, (1999), Behav. Brain Res. **104**, 147-155). These data suggest that novel

H3 antagonists and/or inverse agonists such as the current series could be useful for the treatment of cognitive impairments in neurological diseases such as Alzheimer's disease and related neurodegenerative disorders.

The present invention provides, in a first aspect, a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I)

wherein:

R^1 represents -C_{3-7} cycloalkyl optionally substituted by C_{1-3} alkyl;

R^2 represents -aryl, -heterocyclyl, -heteroaryl, -aryl-X-C_{3-8} cycloalkyl, -aryl-X-aryl, -aryl-X-heteroaryl, -aryl-X-heterocyclyl, -heteroaryl-X-C_{3-8} cycloalkyl, -heteroaryl-X-aryl, -heteroaryl-X-heteroaryl, -heteroaryl-X-heterocyclyl, -heterocyclyl-X-C_{3-8} cycloalkyl, -heterocyclyl-X-aryl, -heterocyclyl-X-heteroaryl or -heterocyclyl-X-heterocyclyl;

X represents a bond, O, CO, -CH_2O-, -$COCH_2$-, -$COCH_2O$-, -$CONR^{2b}$-, -$COCH_2NR^{2b}CO$-, -CSNH-, SO_2, -SO_2C_{1-3} alkyl-, -SO_2C_{2-3} alkenyl-, -COC_{2-3} alkenyl-, -CO-$C(R^{2a})(R^{2b})$- or -CO-$C(R^{2a})(R^{2b})CH_2$-;

R^{2a} represents hydrogen or C_{1-6} alkyl;

R^{2b} represents hydrogen, C_{1-6} alkyl, aryl, heteroaryl, heterocyclyl or C_{1-6} alkylamido;

R^3 represents halogen, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino or trifluoromethyl;

n is 0, 1 or 2;

wherein said alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl groups of R^2 may be optionally substituted by one or more substituents (eg. 1, 2 or 3) which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, cyano, nitro, =O, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, C_{1-6} alkyl, hydroxyC_{1-6} alkyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, sulfonyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, aryloxy, C_{1-6} alkylsulfonamido, C_{1-6} alkylamino, C_{1-6} alkylamido, -R^5, -CO_2R^5, -COR^5, -C_{1-6} alkyl-COR^5, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, arylC_{1-6} alkyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group –NR^6R^7, –C_{1-6} alkyl-NR^6R^7, –C_{3-8} cycloalkyl-NR^6R^7, -$CONR^6R^7$, -NR^6COR^7, -$NR^6SO_2R^7$, -$OCONR^6R^7$, -$NR^6CO_2R^7$, -$NR^5CONR^6R^7$ or -$SO_2NR^6R^7$ (wherein R^5, R^6 and R^7 independently represent hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, -C_{3-8} cycloalkyl, -C_{1-6} alkyl-C_{3-8} cycloalkyl, aryl, -C_{1-6} alkyl-aryl, heterocyclyl or heteroaryl, or wherein –NR^6R^7 may represent a nitrogen containing heterocyclyl group, and wherein said R^5, R^6 and R^7 groups may be optionally substituted by one or more substituents (eg. 1, 2 or 3) which may be the same or different, and which are selected

from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino, =O or trifluoromethyl);
or solvates thereof.

In one aspect of the invention, the substituents present on the alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl groups of R^2 are selected from the group consisting of halogen, hydroxy, cyano, nitro, =O, haloC_{1-6} alkyl, haloC_{1-6} alkoxy, C_{1-6} alkyl, C_{1-6} alkoxy, arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkanoyl, C_{1-6} alkoxycarbonyl, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, sulfonyl, arylsulfonyl, arylsulfonyloxy, arylsulfonylC_{1-6} alkyl, aryloxy, C_{1-6} alkylsulfonamido, C_{1-6} alkylamino, C_{1-6} alkylamido, $-R^5$, $-CO_2R^5$, $-COR^5$, $-C_{1-6}$ alkyl-COR^5, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, arylsulfonamido, arylcarboxamido, arylsulfonamidoC_{1-6} alkyl, arylcarboxamidoC_{1-6} alkyl, aroyl, arylC_{1-6} alkyl, aroylC_{1-6} alkyl, arylC_{1-6} alkanoyl, or a group $-NR^6R^7$, $-C_{1-6}$ alkyl-NR^6R^7, $-C_{3-8}$ cycloalkyl-NR^6R^7, $-CONR^6R^7$, $-NR^6COR^7$, $-NR^6SO_2R^7$, $-OCONR^6R^7$, $-NR^6CO_2R^7$, $-NR^5CONR^6R^7$ or $-SO_2NR^6R^7$ (wherein R^5, R^6 and R^7 independently represent hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl-C_{3-8} cycloalkyl, aryl, heterocyclyl or heteroaryl, or wherein $-NR^6R^7$ may represent a nitrogen containing heterocyclyl group, and wherein said R^5, R^6 and R^7 groups may be optionally substituted by one or more substituents (eg. 1, 2 or 3) which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino, =O or trifluoromethyl).

In a further aspect of the invention, the substituents present on the alkyl, cycloalkyl, aryl, heteroaryl and heterocyclyl groups of R^2 are selected from the group consisting of halogen, hydroxy, cyano, nitro, =O, haloC_{1-6} alkoxy, C_{1-6} alkoxy, hydroxyC_{1-6} alkyl, unsubstituted arylC_{1-6} alkoxy, C_{1-6} alkylthio, C_{1-6} alkoxyC_{1-6} alkyl, C_{3-7} cycloalkylC_{1-6} alkoxy, C_{1-6} alkylsulfonyl, C_{1-6} alkylsulfinyl, C_{1-6} alkylsulfonyloxy, C_{1-6} alkylsulfonylC_{1-6} alkyl, sulfonyl, unsubstituted arylsulfonyl, unsubstituted arylsulfonyloxy, unsubstituted arylsulfonylC_{1-6} alkyl, unsubstituted aryloxy, C_{1-6} alkylsulfonamido, C_{1-6} alkylamino, C_{1-6} alkylamido, $-R^5$, $-CO_2R^5$, $-COR^5$, $-C_{1-6}$ alkyl-COR^5, C_{1-6} alkylsulfonamidoC_{1-6} alkyl, C_{1-6} alkylamidoC_{1-6} alkyl, unsubstituted arylsulfonamido, unsubstituted arylcarboxamido, unsubstituted arylsulfonamidoC_{1-6} alkyl, unsubstituted arylcarboxamidoC_{1-6} alkyl, unsubstituted arylcarbonylC_{1-6} alkyl, or a group $-NR^6R^7$, $-C_{1-6}$ alkyl-NR^6R^7, $-C_{3-8}$ cycloalkyl-NR^6R^7, $-CONR^6R^7$, $-NR^6COR^7$, $-NR^6SO_2R^7$, $-OCONR^6R^7$, $-NR^6CO_2R^7$, $-NR^5CONR^6R^7$ or $-SO_2NR^6R^7$ (wherein R^5, R^6 and R^7 independently represent hydrogen, C_{1-6} alkyl, haloC_{1-6} alkyl, $-C_{3-8}$ cycloalkyl, $-C_{1-6}$ alkyl-C_{3-8} cycloalkyl, aryl, $-C_{1-6}$ alkyl-aryl, heterocyclyl or heteroaryl, or wherein $-NR^6R^7$ may represent a nitrogen containing heterocyclyl group, and wherein said R^5, R^6 and R^7 groups may be optionally substituted by one or more substituents (eg. 1, 2 or 3) which may be the same or different, and which are selected from the group consisting of halogen, hydroxy, C_{1-6} alkyl, C_{1-6} alkoxy, cyano, amino, =O or trifluoromethyl).

In the context of the present invention, a -C_{1-6} alkylamidoC_{1-6} alkyl group includes a -C_{1-6} alkyl-CO-NH-C_{1-6} alkyl group and a -C_{1-6} alkyl-NH-CO-C_{1-6} alkyl group.

In a further aspect of the invention, X represents a bond, O, CO, -CH_2O-, -$COCH_2$-, -$COCH_2O$-, -$CONR^{2b}$-, -$COCH_2NR^{2b}CO$-, SO_2, -SO_2C_{1-3} alkyl-, -SO_2C_{2-3} alkenyl-, -COC_{2-3} alkenyl-, -CO-$C(R^{2a})(R^{2b})$- or -CO-$C(R^{2a})(R^{2b})CH_2$-.

Alkyl groups, whether alone or as part of another group, may be straight chain or branched and the groups alkoxy and alkanoyl shall be interpreted similarly. Alkyl moieties are more preferably C_{1-4} alkyl, eg. methyl or ethyl. The term 'halogen' is used herein to describe, unless otherwise stated, a group selected from fluorine, chlorine, bromine or iodine.

References to 'aryl' include references to monocyclic carbocyclic aromatic rings (eg. phenyl) and bicyclic carbocyclic aromatic rings (e.g. naphthyl) or carbocyclic benzofused rings (eg. C_{3-8} cycloalkyl fused to a phenyl ring, such as dihydroindenyl or tetrahydronaphthalenyl).

The term "heterocyclyl" is intended to mean a 4-7 membered monocyclic saturated or partially unsaturated aliphatic ring or a 4-7 membered saturated or partially unsaturated aliphatic ring fused to a benzene ring, which aliphatic ring contains 1 to 3 heteroatoms selected from oxygen, nitrogen or sulphur. Suitable examples of such monocyclic rings include pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiomorpholinyl, tetrahydrofuranyl, tetrahydropyranyl, diazepanyl, azepanyl, imidazolidinyl, isothiazolidinyl, oxazolidinyl, pyrrolidinone and tetrahydro-oxazepinyl. Suitable examples of benzofused heterocyclic rings include indolinyl, isoindolinyl, benzodioxolyl, dihydroisoindole, dihydrobenzofuranyl, dihydrobenzothiopyranyl, dihydroisoquinolinyl, dihydrobenzoxazinyl, dihydrobenzodioxazinyl, dihydrodioxolyl and dihydrochromenyl.

The term "heteroaryl" is intended to mean a 5-7 membered monocyclic aromatic or a fused 8-11 membered bicyclic aromatic ring, which monocyclic or bicyclic ring contains 1 to 3 heteroatoms selected from oxygen, nitrogen and sulphur. Suitable examples of such monocyclic aromatic rings include thienyl, furyl, pyrrolyl, triazolyl, imidazolyl, oxazolyl, thiazolyl, oxadiazolyl, isothiazolyl, isoxazolyl, thiadiazolyl, pyrazolyl, pyrimidyl, pyridazinyl, pyrazinyl, pyridyl and tetrahydropyranyl. Suitable examples of such fused aromatic rings include benzofused aromatic rings such as quinolinyl, isoquinolinyl, quinazolinyl, quinoxalinyl, cinnolinyl, naphthyridinyl, indolyl, indazolyl, furopyridinyl, pyrrolopyridinyl, benzofuranyl, benzothienyl, benzimidazolyl, benzoxazolyl, benzisoxazolyl, benzothiazolyl, benzisothiazolyl, benzoxadiazolyl, benzothiadiazolyl and the like. Suitable examples of such fused heteroaryl rings include thienopyridinyl, pyrazolopyrimidinyl, pyrazolopyridinyl, thienopyrazolyl and imidazothiazolyl.

In one aspect, R^1 represents -C_{3-7} cycloalkyl (eg. cyclobutyl, cyclopentyl or cyclohexyl) optionally substituted by a C_{1-3} alkyl (eg. methyl) group.

In a more particular aspect, R^1 represents unsubstituted cyclobutyl or cyclopentyl, especially unsubstituted cyclobutyl.

In one embodiment, R^2 represents

-aryl (eg. -phenyl) optionally substituted by one or more halogen (eg. fluorine), cyano, C_{1-6} alkyl (eg. methyl) -$CONR^6R^7$ (eg. –CON(H)(Me)), C_{1-6} alkylamidoC_{1-6} alkyl (eg. –$CH_2CON(H)(Me)$) or -C_{1-6} alkyl-COR^5 (eg. –CH_2-COMe) groups;

-aryl-X-heteroaryl (eg. –phenyl-O-pyridinyl or -phenyl-CONH-pyridinyl) optionally substituted by one or more –$CONR^6R^7$ groups (eg. –CON(H)(Me));

-heteroaryl (eg. –pyridinyl, -thiazolyl or -furanyl) optionally substituted by one or more cyano, -CO_2R^5 (eg. -CO_2H or -CO_2CH_3), –$CONR^6R^7$ (eg. –CON(H)(Me)) or alkylamidoalkyl (eg. $CH_2CON(H)Me$) groups;

-heteroaryl-X-heterocyclyl (eg. –pyridinyl-CO-morpholinyl);

-heterocyclyl (eg. piperazinyl, piperidinyl or oxazolidinyl) optionally substituted by one or more –$SO_2NR^6R^7$ (eg. –$SO_2N(Me)_2$), sulfonyl, haloC_{1-6} alkyl (eg. –CH_2CF_3), C_{1-6} alkylsulfonyl (eg. –SO_2Me or –$SO_2CH(Me)_2$), C_{1-6} alkoxycarbonyl (eg. –$COCH_2OCH(Me)_2$), –COR^5 (eg. –CO-CH_2-$C(Me)_3$), CO_2R^5 (eg. -CO_2CH_2phenyl), =O or hydroxyalkyl (eg. hydroxymethyl) groups;

-heterocyclyl-X-C_{3-8} cycloalkyl (eg. –piperazinyl-CO-cyclopentyl, -piperazinyl-CO-cyclopropyl or –piperazinyl-CO-cyclohexyl) optionally substituted by one or more C_{1-6} alkoxy (eg. –$OC(CH_3)_3$) groups;

-heterocyclyl-X-aryl (eg. –piperidinyl-CO-phenyl, -piperazinyl-phenyl, -piperazinyl-CO-phenyl, -piperazinyl-SO_2-phenyl, -piperazinyl-CO-naphthyl, -piperazinyl-SO_2-naphthyl, -piperazinyl-$COCH_2$-phenyl, -piperazinyl-$COCH_2$-naphthyl, -piperazinyl-$COCH_2O$-phenyl, -piperazinyl-CONH-phenyl, -piperazinyl-$COCH_2NHCO$-phenyl, -piperazinyl-SO_2CH_2-phenyl, -piperazinyl-$SO_2(CH_2)_2$-phenyl, -piperazinyl-$SO_2(CH_2)_2$-naphthyl, -piperazinyl-SO_2-CH=CH-phenyl, -piperazinyl-CO-CH=CH-phenyl, -piperazinyl-CO-dihydroindenyl, -piperazinyl-CO-C(H)(Me)-phenyl, -piperazinyl-CO-$CH(NHCOCH_3)$-phenyl, -piperazinyl-CO-CH(phenyl)-phenyl, -piperazinyl-CO-C(H)(Et)-CH_2-phenyl, –oxazolidinyl-CH_2O-phenyl, -piperidinyl-phenyl, -piperidinyl-CONH-phenyl, piperidinyl-CSNH-phenyl or -piperazinyl-CO-naphthyl) optionally substituted by one or more halogen (eg. chlorine, fluorine or bromine), hydroxy, cyano, nitro, =O, C_{1-6} alkyl (eg. methyl, ethyl, -$CH(Me)_2$ or –$C(Me)_3$), haloC_{1-6} alkyl (eg. trifluoromethyl), C_{1-6} alkoxy (eg. methoxy or –$OCH(Me)_2$), haloC_{1-6} alkoxy (eg. trifluoromethoxy), -R^5 (eg. phenyl, pyridinyl, furanyl, pyrazolyl or oxadiazolyl optionally substituted by one or more C_{1-6} alkyl (eg. methyl) groups), -COR^5 (eg. –CO-methyl, -CO-ethyl, -CO-trifluoromethyl, –CO-phenyl or –CO-piperidinyl), -CO_2R^5 (eg. –COOH), aryloxy (eg. –O-phenyl), C_{1-6} alkylsulfonyl (eg. –SO_2Me), -NR^6R^7 (eg. –$N(Me)_2$) –NR^6COR^7 (eg. –NHCOMe) groups;

-heterocyclyl-X-heterocyclyl (eg. –piperazinyl-CO-piperidinyl, -piperazinyl-CO-morpholinyl, -piperazinyl-CO-tetrahydropyranyl, -piperazinyl-CO-pyrrolidinyl, -piperazinyl-CO-dihydrochromenyl, -piperazinyl-SO_2-dihydrochromenyl, -piperazinyl-CO-dihydrobenzothiopyranyl, -piperazinyl-CO-dihydrobenzofuranyl, -piperazinyl-SO_2-dihydrobenzofuranyl, -piperazinyl-SO_2-dihydrobenzoxazinyl, -piperazinyl-SO_2-dihydrobenzodioxinyl, -piperazinyl-$COCH_2$-dihydroisoindolyl, -piperazinyl-$COCH_2$-dihydrobenzodioxolyl, -piperazinyl-$COCH_2$-piperidinyl, -piperidinyl-CO-tetrahydropyranyl or piperidinyl-CO-isoindolyl) optionally substituted by one or more C_{1-6} alkyl (eg. methyl or -$CH(Me)_2$) or =O groups; or

-heterocyclyl-X-heteroaryl (eg. –piperazinyl-CO-benzoxadiazolyl, –piperazinyl-SO_2-benzoxadiazolyl, -piperazinyl-CO-thiazolyl, -piperazinyl-$COCH_2$-thiazolyl, -piperazinyl-CO-thienyl, -piperazinyl-CONH-thienyl, -piperazinyl-$COCH_2$-thienyl, -piperazinyl-SO_2-thienyl, -piperazinyl-CO-quinolinyl, -piperazinyl-$COCH_2$-quinolinyl, -piperazinyl-SO_2-quinolinyl, -piperazinyl-CO-isoquinolinyl, -piperazinyl-SO_2-isoquinolinyl, -piperazinyl-CO-imidazolyl, -piperazinyl-$COCH_2$-imidazolyl, -piperazinyl-SO_2-imidazolyl, -piperazinyl-SO_2-thiazolyl, -piperazinyl-CO-pyrazolyl, -piperazinyl-SO_2-pyrazolyl, -piperazinyl-CO-benzothienyl, -piperazinyl-SO_2-benzothienyl, -piperazinyl-$COCH_2$-benzothienyl, -piperazinyl-SO_2-thienopyridinyl, -piperazinyl-CO-benzofuranyl, -piperazinyl-CO-oxadiazolyl, -piperazinyl-CO-indazolyl, -piperazinyl-CO-pyrazolopyrimidinyl, -piperazinyl-CO-oxazolyl, -piperazinyl-CO-thienopyrazolyl, -piperazinyl-CO-pyrazolopyridinyl, -piperazinyl-CO-benzothiazolyl, -piperazinyl-CO-furanyl, -piperazinyl-CO-indolyl, -piperazinyl-CO-pyridinyl, -piperazinyl-$COCH_2$-pyridinyl, -piperazinyl-SO_2-imidazothiazolyl, -piperazinyl-$COCH_2$-imidazothiazolyl, -piperazinyl-SO_2-isoxazolyl, -piperazinyl-CO-isoxazolyl, -piperazinyl-SO_2-pyridinyl, -piperazinyl-SO_2-pyridinyl or –piperazinyl-SO_2-benzothiadiazolyl, -piperidinyl-CO-pyridinyl, -piperidinyl-CO-pyrazinyl, -piperidinyl-CO-benzoxadiazolyl, -piperidinyl-CO-thiazolyl, -piperidinyl-pyridinyl, -piperidinyl-pyrazinyl, -piperidinyl-CONH-pyridinyl, piperidinyl-CO-quinoxalinyl or –piperidinyl-CO-pyrazolopyramidinyl) optionally substituted by one or more halogen (eg. chlorine), cyano, C_{1-6} alkyl (eg. methyl), haloC_{1-6}alkyl (eg. -CF_3) =O, -R^5 (eg. phenyl, isoxazolyl, oxazolyl or pyridinyl), -CO_2R^5 (eg. -CO_2H, -CO_2CH_3 or -$CO_2C(CH_3)_3$), -NR^6R^7 (eg. pyrrolidinone). –$CONR^6R^7$ (eg. -CON(H)CH_3)) aryloxy (eg. –O-phenyl), -NR^6COR^7 (eg. –NHCOMe) or arylC_{1-6} alkyl (eg. –CH_2-phenyl) groups.

In embodiments where R^2 is a substituted nitrogen containing heterocyclyl group, the nitrogen containing heterocyclyl group (eg. piperidinyl or piperazinyl) is typically substituted at the nitrogen atom.

Where R^2 represents –heterocyclyl-X-aryl, -heterocyclyl-X-heterocyclyl or -heterocyclyl-X-heteroaryl in which the heterocyclyl group attached to the tetrahydrobenzazepine contains one or more nitrogen atoms (e.g. piperidinyl or piperazinyl), the heterocyclyl group attached to the tetrahydrobenzazepine is typically linked to X through a nitrogen atom.

In a more particular embodiment, R^2 represents

-aryl-X-heteroaryl (eg. –phenyl-O-pyridinyl) optionally substituted by a $–CONR^6R^7$ group (eg. –CON(H)(Me)); or

-heterocyclyl-X-aryl (eg. –piperidinyl-CO-phenyl) optionally substituted by a cyano group.

In a most particular embodiment, R^2 represents

-heterocyclyl-X-aryl (eg. –piperidinyl-CO-phenyl) optionally substituted by a cyano group.

In one aspect,X represents a bond, O, CO, $-CH_2O-$, $-COCH_2-$, $-COCH_2O-$, $-CONR^{2b}-$ (eg. -CONH-), $-COCH_2NR^{2b}CO-$ (eg. $-COCH_2NHCO-$), SO_2, $-SO_2C_{1-3}$ alkyl- (eg. $–SO_2-CH_2-$ or $–SO_2-(CH_2)_2-$), $-SO_2C_{2-3}$ alkenyl- (eg. $–SO_2-CH=CH-$), $-COC_{2-3}$ alkenyl- (eg. –CO-CH=CH-), $-CO-C(R^{2a})(R^{2b})-$ (eg. –CO-C(H)(Me), –CO-C(H)(phenyl) or –CO-C(H)(NHCOMe)) or $-CO-C(R^{2a})(R^{2b})CH_2-$ (eg. –CO-C(H)(Et)-CH_2-).

In a more particular aspect, X represents a bond, SO_2, CO or O, most preferably CO.

In a further aspect, R^{2a} represents hydrogen and R^{2b} represents C_{1-6} alkyl (eg. methyl or ethyl), aryl (eg. phenyl) or C_{1-6} alkylamido (eg. –NHCOMe).

In another embodiment, R^5 represents hydrogen, C_{1-6} alkyl (eg. methyl, ethyl or $-CH_2-C(Me)_3$), haloC_{1-6} alkyl (eg. trifluoromethyl), aryl (eg. phenyl), heterocyclyl (eg. piperidinyl), heteroaryl (eg. furanyl, pyridinyl, pyrazolyl, isoxazolyl, oxazolyl, oxadiazolyl) optionally substituted by one or more C_{1-6} alkyl (eg. methyl) groups.

In a further aspect, R^6 and R^7 independently represent hydrogen or C_{1-6} alkyl (eg. methyl).

In a further aspect, n represents 0 or 1, more preferably 0.

When n represents 1, R^3 is preferably a halogen (eg. iodine) atom or a cyano group.

Compounds according to the invention include examples E1-E262 as shown below, or a pharmaceutically acceptable salt thereof.

One compound according to the invention includes 6-{[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)phenyl]oxy}-N-methyl-3-pyridinecarboxamide or a pharmaceutically acceptable salt thereof.

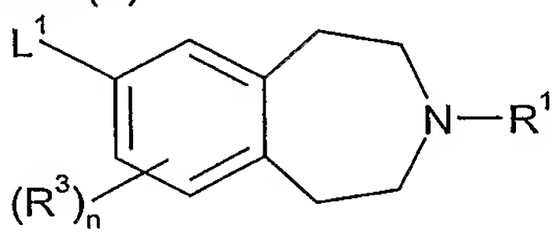
Another compound according to the invention is 4-{[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]carbonyl}benzonitrile or a pharmaceutically acceptable salt thereof.

Compounds of formula (I) may form acid addition salts with acids, such as conventional pharmaceutically acceptable acids, for example maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, sulphate, citric, lactic, mandelic, tartaric and methanesulphonic. Salts, solvates and hydrates of compounds of formula (I) therefore form an aspect of the invention.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of these compounds and the mixtures thereof including racemates. Tautomers also form an aspect of the invention.

The present invention also provides a process for the preparation of a compound of formula (I) or a pharmaceutically acceptable salt thereof, which process comprises:

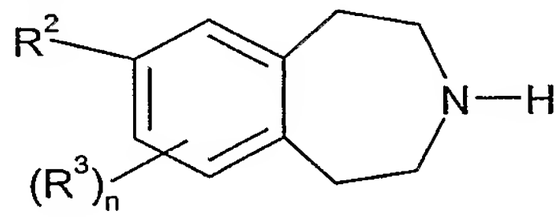
(a) reacting a compound of formula (II)



(II)

wherein R^1, R^3 and n are as defined above and L^1 represents a suitable leaving group such as a halogen atom (eg. bromine or iodine), or an optionally activated hydroxyl group (such as a triflate group) with a compound of formula R^2-Y, wherein R^2 is as defined above for R^2 and Y represents hydrogen or a suitable coupling group such as a boronic acid or organometallic group such as zinc or alkyl stannane; or

(b) reacting a compound of formula (III)



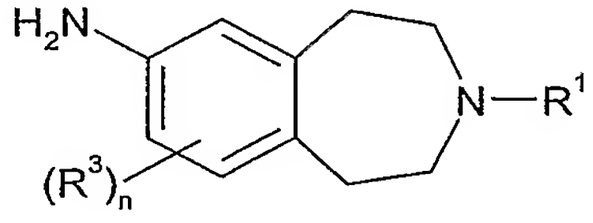
(III)

wherein R^2, R^3 and n are as defined above, with a compound of formula R^1-L^2, wherein R^1 is as defined above and L^2 represents a suitable leaving group such as a halogen atom (eg. bromine, iodine or tosylate); or

(c) reacting a compound of formula (III) as defined above, with a ketone of formula $R^{1'}$=O, wherein $R^{1'}$is C_{3-7} cycloalkyl optionally substituted by C_{1-3} alkyl; or

(d) preparing a compound of formula (I) wherein R^2 represents -heterocyclyl, wherein said heterocyclyl is a 1,3-oxazolidin-2-one group substituted at the 5-position with a hydroxymethyl group, and wherein the oxazolidin-2-one group is attached to the

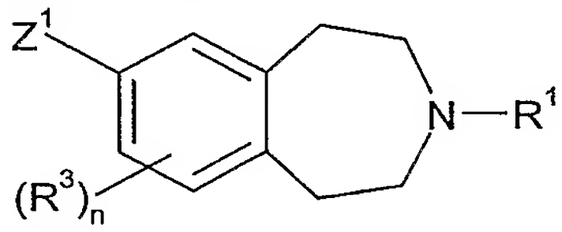
benzazepine moiety through the nitrogen atom, which comprises reacting a compound of formula (IV)



(IV)

in a two step process, wherein R^1, R^3 and n are as defined above, with a benzyl chloroformate group and then glycidol butyrate; or

(e) preparing a compound of formula (I) wherein R^2 represents -aryl, -heteroaryl, -aryl-X-C_{3-8} cycloalkyl, -aryl-X-aryl, -aryl-X-heteroaryl, -aryl-X-heterocyclyl, -heteroaryl-X-C_{3-8} cycloalkyl, -heteroaryl-X-aryl, -heteroaryl-X-heteroaryl, -heteroaryl-X-heterocyclyl, which comprises reacting a compound of formula (XI)



(XI)

wherein R^1, R^3 and n are as defined above and Z^1 represents a suitable coupling group such as a boronic acid or ester, or organometallic group such as zinc or alkyl stannane with a compound of formula $R^{2"}$-L^1, wherein L^1 represents a suitable leaving group such as a halogen atom (eg. bromine or iodine), or an optionally activated hydroxyl group (such as a triflate group) and $R^{2"}$ represents the groups -aryl, -heteroaryl, -aryl-X-C_{3-8} cycloalkyl, -aryl-X-aryl, -aryl-X-heteroaryl, -aryl-X-heterocyclyl, -heteroaryl-X-C_{3-8} cycloalkyl, -heteroaryl-X-aryl, -heteroaryl-X-heteroaryl, -heteroaryl-X-heterocyclyl, or

(f) deprotecting a compound of formula (I) which is protected; or

(g) interconversion from another compound of formula (I).

When the compound of formula (II) represents an aryl electrophilic system, i.e. L^1 is a halogen atom (eg. bromine or iodine) or triflate group and R^2-Y is a boronic acid (or ester), process (a) typically comprises the use of a palladium catalyst such as tetrakis(triphenylphosphine)palladium, in an appropriate solvent such as toluene or DME, with an appropriate base such as aqueous sodium carbonate at an appropriate temperature such as reflux.

When R^2-Y is an amine, for example piperazine, process (a) typically comprises the use of a palladium catalyst such as palladium acetate, with an appropriate ligand such as o-biphenyl di-tert-butylphosphine in an appropriate solvent such as DME, with an appropriate base such as potassium phosphate, at an appropriate temperature such as reflux.

Process (b) typically comprises the use of a suitable base, such as potassium carbonate in an appropriate solvent such as 2-butanone optionally in the presence of a transfer reagent such as potassium iodide at an appropriate temperature such as reflux.

Process (c) typically comprises the use of reductive conditions (such as treatment with a borohydride eg. sodium triacetoxyborohydride), optionally in the presence of an acid, such as acetic acid, in an appropriate solvent such as dichloromethane at a suitable temperature such as room temperature.

Step 1 of process (d) typically comprises the use of a chloroformate such as benzyl chloroformate, with suitable base, such as sodium hydrogen carbonate in an appropriate solvent such as acetone. Step 2 of process (d) involves reacting the product of step 1 with glycidol butyrate according to WO 02/059115.

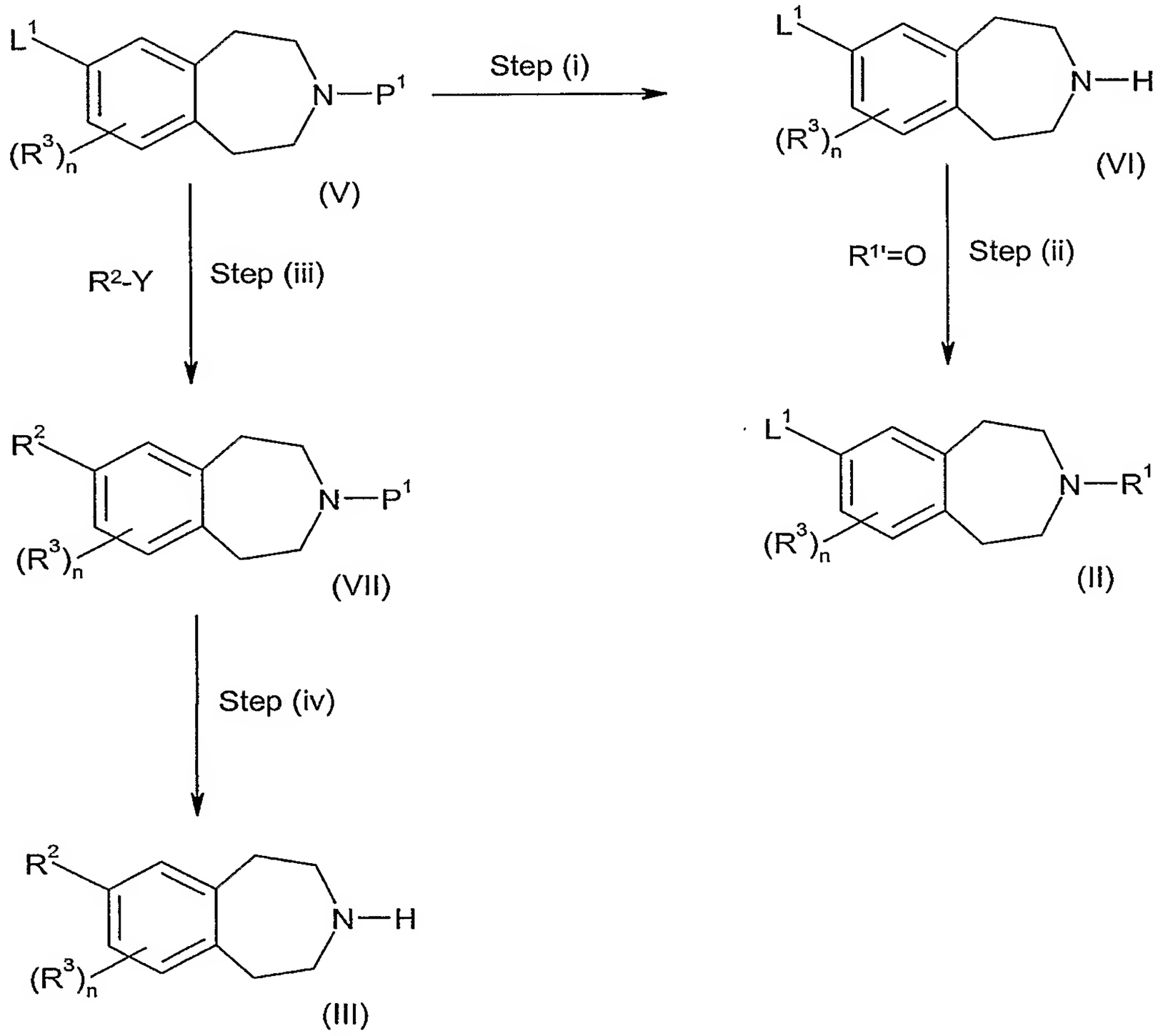
When the compound of formula (XI) represents an aryl boronic acid (or ester) and $R^{2''}$-L^1 is an electrophilic aryl or heteroaryl system, i.e. L^1 is a halogen atom (eg. bromine or iodine) or triflate group, process (e) typically comprises the use of a palladium catalyst such as tetrakis(triphenylphosphine)palladium, in an appropriate solvent such as toluene, with an appropriate base such as aqueous sodium carbonate at an appropriate temperature such as reflux.

In process (f), examples of protecting groups and the means for their removal can be found in T. W. Greene 'Protective Groups in Organic Synthesis' (J. Wiley and Sons, 1991). Suitable amine protecting groups include sulphonyl (e.g. tosyl), acyl (e.g. acetyl, 2',2',2'-trichloroethoxycarbonyl, benzyloxycarbonyl or t-butoxycarbonyl) and arylalkyl (e.g. benzyl), which may be removed by hydrolysis (e.g. using an acid such as hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane) or reductively (e.g. hydrogenolysis of a benzyl group or reductive removal of a 2',2',2'-trichloroethoxycarbonyl group using zinc in acetic acid) as appropriate. Where the protecting group is benzyloxycarbonyl, this may be removed by hydrogenolysis using a suitable catalyst such as palladium on charcoal, at a suitable temperature (eg. room temperature) and at a suitable pressure of hydrogen (eg. atmospheric pressure) in a suitable solvent (eg. ethanol:methanol (1:1) or ethanol). Other suitable amine protecting groups include trifluoroacetyl (-$COCF_3$) which may be removed by base catalysed hydrolysis or a solid phase resin bound benzyl group, such as a Merrifield resin bound 2,6-dimethoxybenzyl group (Ellman linker), which may be removed by acid catalysed hydrolysis, for example with trifluoroacetic acid.

Process (g) may be performed using conventional interconversion procedures such as epimerisation, oxidation, reduction, alkylation, nucleophilic or electrophilic aromatic substitution, ester hydrolysis, amide bond formation or transition metal mediated coupling reactions. An example of a reduction reaction useful as an interconversion procedure

would include the conversion of a heteroaryl group, such as a pyridyl group, to a heterocycyl group, for example a piperidyl group, using a catalyst system such as platinum oxide in the presence of hydrogen. Examples of transition metal mediated coupling reactions useful as interconversion procedures include the following: Palladium catalysed coupling reactions between organic electrophiles, such as aryl halides, and organometallic reagents, for example boronic acids (Suzuki cross-coupling reactions); Palladium catalysed amination and amidation reactions between organic electrophiles, such as aryl halides, and nucleophiles, such as amines and amides; Copper catalysed amidation reactions between organic electrophiles (such as aryl halides) and nucleophiles such as amides; and Copper mediated coupling reactions between phenols and boronic acids.

Compounds of formula (II) and (III) may be prepared in accordance with the following scheme:



wherein R^1, $R^{1'}$, $R^{2,}$, R^3, n, Y and L^1 are as defined above and P^1 represents a suitable protecting group such as Boc.

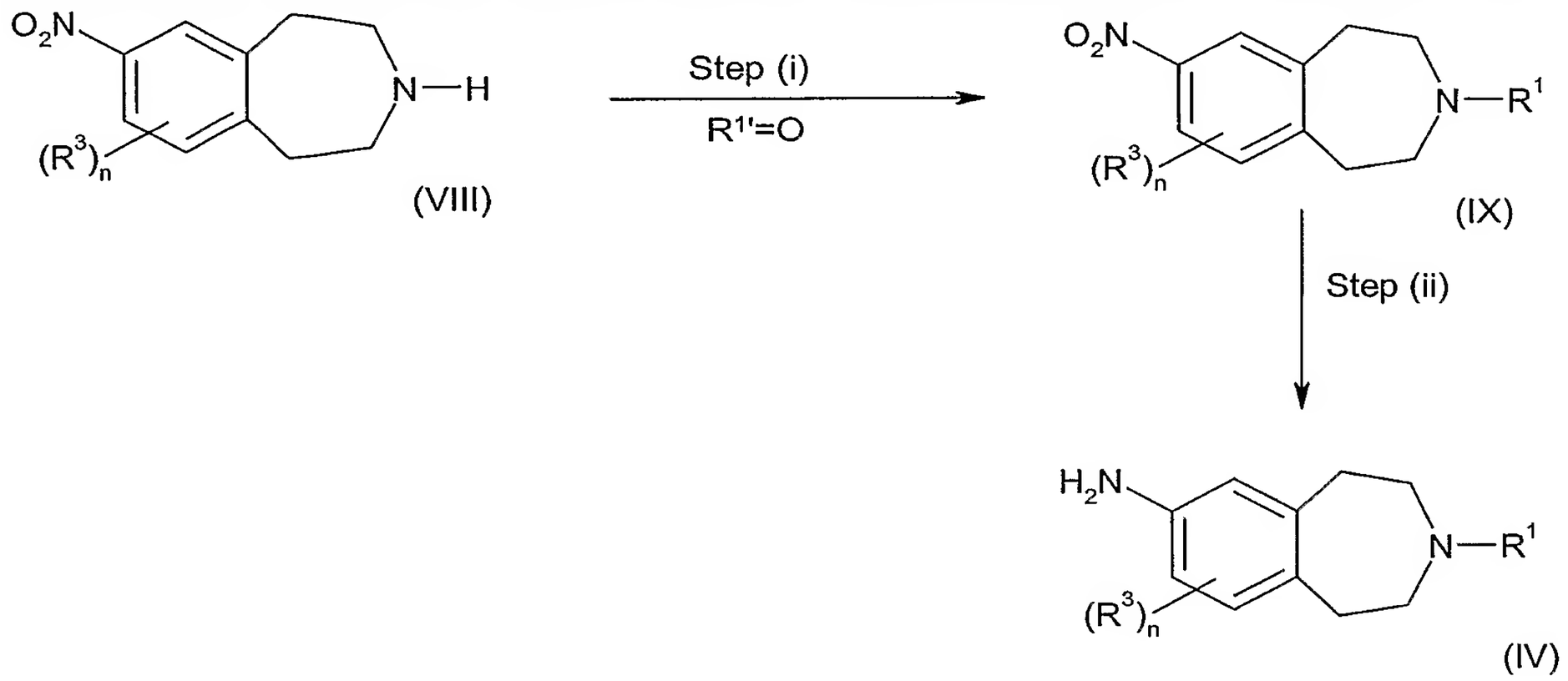
Step (i) typically comprises a deprotection reaction, for example, when P^1 represents Boc the deprotection reaction comprises reaction of a compound of formula (V) with an acid, for example hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane.

Step (ii) may be performed under reducing conditions in an analogous manner to that described for process (c) above.

Step (iii) may be performed in an analogous manner to that described for process (a) above.

Step (iv) typically comprises a deprotection reaction to provide a compound of formula (III) and can be performed as described in step (i) above.

Compounds of formula (IV) may be prepared in accordance with the following scheme:

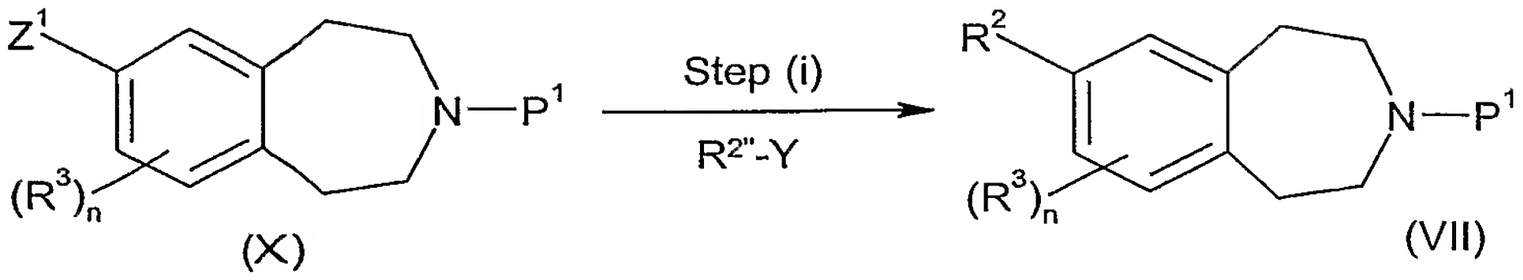


wherein R^1, $R^{1'}$, R^3 and n are as defined above.

Step (i) may be performed under reducing conditions in an analogous manner to that described for process (c) above. Alternatively, step (i) may be performed by reacting the compound of formula (VIII) with a compound of formula R^1-L^2, wherein R^1 is defined above and L^2 represents a suitable leaving group such as a halogen atom (eg. bromine, iodine or tosylate), in an analogous manner to that described for process (b) above.

Step (ii) typically comprises a hydrogenation reaction comprising 10% palladium on carbon paste in the presence of suitable solvents such as methanol and tetrahydrofuran.

Compounds of formula (VII) may also be prepared in accordance with the following scheme:

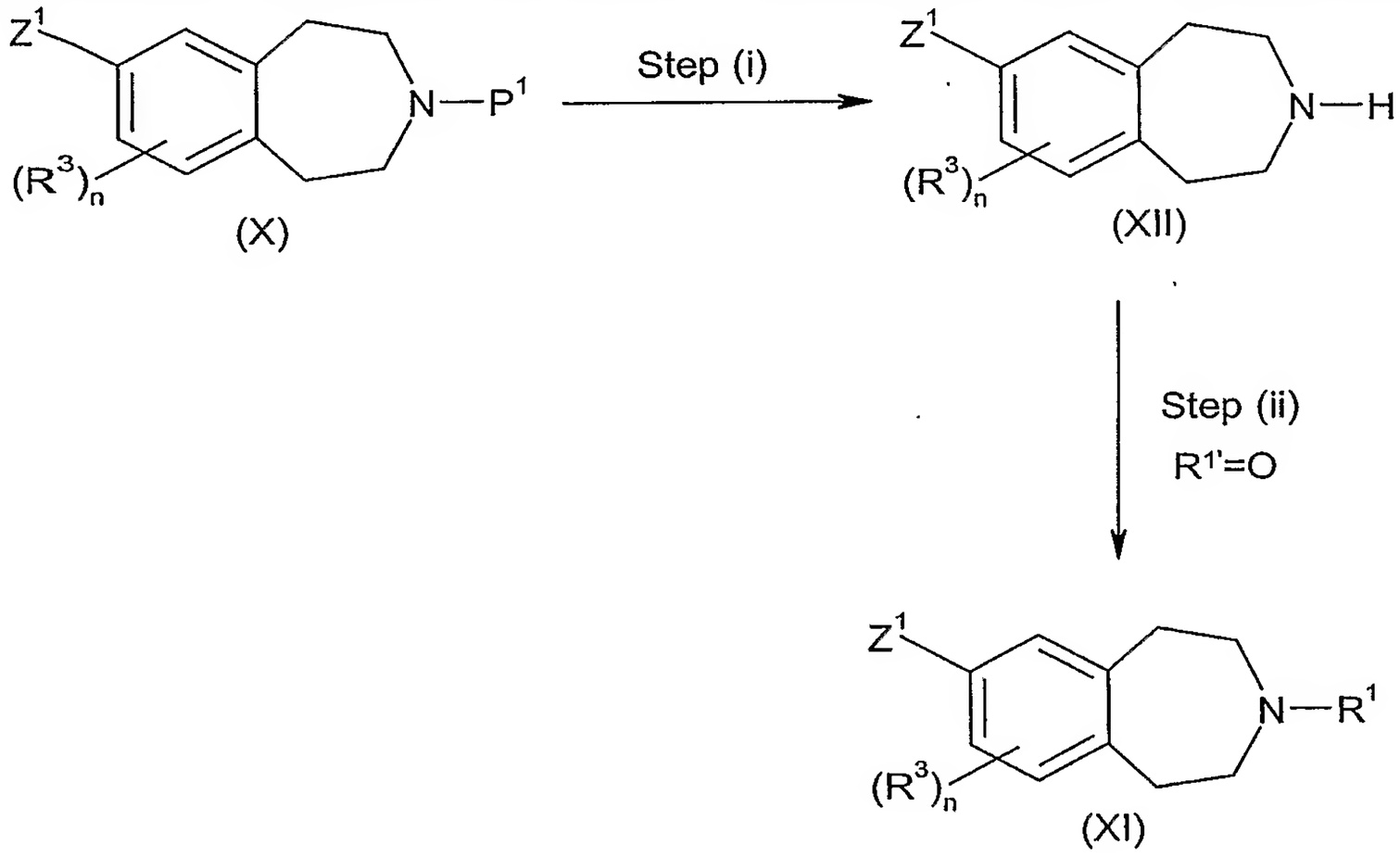


(X) (VII)

wherein R^2 represents -aryl, -heteroaryl, -aryl-X-C_{3-8} cycloalkyl, -aryl-X-aryl, -aryl-X-heteroaryl, -aryl-X-heterocyclyl, -heteroaryl-X-C_{3-8} cycloalkyl, -heteroaryl-X-aryl, -heteroaryl-X-heteroaryl, -heteroaryl-X-heterocyclyl, wherein $R^{2"}$, R^3 and n are as defined above and wherein P^1 represents a suitable protecting group such as Boc and Z^1 represents a boronic ester or boronic acid or any other group suitable for transition metal mediated cross coupling reactions.

Step (i) may be performed with the use of a palladium catalyst such as tetrakis(triphenylphosphine)palladium, in an appropriate solvent such as toluene, with an appropriate base such as sodium carbonate at an appropriate temperature such as reflux.

Compounds of formula (XI) may be prepared in accordance with the following scheme:



(X) (XII) (XI)

wherein R^1, $R^{1'}$, R^3 and n are as defined above and P^1 represents a suitable protecting group such as Boc and Z^1 represents a boronic ester or boronic acid or any other group suitable for transition metal mediated cross coupling reactions.

Step (i) typically comprises a deprotection reaction, for example, when P^1 represents Boc the deprotection reaction comprises reaction of a compound of formula (V) with an acid, for example hydrochloric acid in dioxan or trifluoroacetic acid in dichloromethane.

Step (ii) may be performed under reducing conditions in an analogous manner to that described for process (c) above. Alternatively, step (ii) may be performed by reacting the compound of formula (XII) with a compound of formula R^1-L^2, wherein R^1 is defined above and L^2 represents a suitable leaving group such as a halogen atom (eg. bromine, iodine or tosylate), in an analogous manner to that described for process (b) above.

Compounds of formula (V) may be prepared in an analogous manner to those described in Description 3 of WO 02/040471.

Compounds of formula (VIII) may be prepared in an analogous manner to those described in WO 03/068752.

Compounds of formula (X) may be prepared in an analogous manner to those described in WO 2004056369 A1 (Example 264, step 1)

Compounds of formula (I) and their pharmaceutically acceptable salts have affinity for and are antagonists and/or inverse agonists of the histamine H3 receptor and are believed to be of potential use in the treatment of neurological diseases including Alzheimer's disease, dementia, age-related memory dysfunction, mild cognitive impairment, cognitive deficit, epilepsy, neuropathic pain, inflammatory pain, migraine, Parkinson's disease, multiple sclerosis, stroke and sleep disorders including narcolepsy; psychiatric disorders including schizophrenia (particularly cognitive deficit of schizophrenia), attention deficit hypereactivity disorder, depression and addiction; and other diseases including obesity, asthma, allergic rhinitis, nasal congestion, chronic obstructive pulmonary disease and gastro-intestinal disorders.

Thus the invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof, for use as a therapeutic substance in the treatment or prophylaxis of the above disorders, in particular cognitive impairments in diseases such as Alzheimer's disease and related neurodegenerative disorders.

The invention further provides a method of treatment or prophylaxis of the above disorders, in mammals including humans, which comprises administering to the sufferer a therapeutically effective amount of a compound of formula (I) or a pharmaceutically acceptable salt thereof.

In another aspect, the invention provides the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof in the manufacture of a medicament for use in the treatment of the above disorders.

When used in therapy, the compounds of formula (I) are usually formulated in a standard pharmaceutical composition. Such compositions can be prepared using standard procedures.

Thus, the present invention further provides a pharmaceutical composition for use in the treatment of the above disorders which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

The present invention further provides a pharmaceutical composition which comprises the compound of formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

Compounds of formula (I) may be used in combination with other therapeutic agents, for example histamine H1 antagonists or medicaments claimed to be useful as either disease modifying or symptomatic treatments of Alzheimer's disease. Suitable examples of such other therapeutic agents may be agents known to modify cholinergic transmission such as 5-HT_6 antagonists, M1 muscarinic agonists, M2 muscarinic antagonists or acetylcholinesterase inhibitors. When the compounds are used in combination with other therapeutic agents, the compounds may be administered either sequentially or simultaneously by any convenient route.

The invention thus provides, in a further aspect, a combination comprising a compound of formula (I) or a pharmaceutically acceptable derivative thereof together with a further therapeutic agent or agents.

The combinations referred to above may conveniently be presented for use in the form of a pharmaceutical formulation and thus pharmaceutical formulations comprising a combination as defined above together with a pharmaceutically acceptable carrier or excipient comprise a further aspect of the invention. The individual components of such combinations may be administered either sequentially or simultaneously in separate or combined pharmaceutical formulations.

When a compound of formula (I) or a pharmaceutically acceptable derivative thereof is used in combination with a second therapeutic agent active against the same disease state the dose of each compound may differ from that when the compound is used alone. Appropriate doses will be readily appreciated by those skilled in the art.

A pharmaceutical composition of the invention, which may be prepared by admixture, suitably at ambient temperature and atmospheric pressure, is usually adapted for oral, parenteral or rectal administration and, as such, may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, injectable or

infusible solutions or suspensions or suppositories. Orally administrable compositions are generally preferred.

Tablets and capsules for oral administration may be in unit dose form, and may contain conventional excipients, such as binding agents, fillers, tabletting lubricants, disintegrants and acceptable wetting agents. The tablets may be coated according to methods well known in normal pharmaceutical practice.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspension, solutions, emulsions, syrups or elixirs, or may be in the form of a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and, if desired, conventional flavourings or colorants.

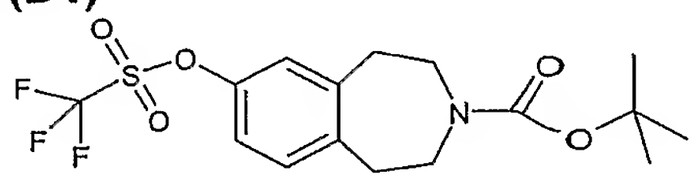
For parenteral administration, fluid unit dosage forms are prepared utilising a compound of the invention or pharmaceutically acceptable salt thereof and a sterile vehicle. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing solutions, the compound can be dissolved for injection and filter sterilised before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. Parenteral suspensions are prepared in substantially the same manner, except that the compound is suspended in the vehicle instead of being dissolved, and sterilisation cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspension in a sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The composition may contain from 0.1% to 99% by weight, preferably from 10 to 60% by weight, of the active material, depending on the method of administration. The dose of the compound used in the treatment of the aforementioned disorders will vary in the usual way with the seriousness of the disorders, the weight of the sufferer, and other similar factors. However, as a general guide suitable unit doses may be 0.05 to 1000 mg, more suitably 1.0 to 200mg, and such unit doses may be administered more than once a day, for example two or three a day. Such therapy may extend for a number of weeks or months.

The following Descriptions and Examples illustrate the preparation of compounds of the invention.

Description 1

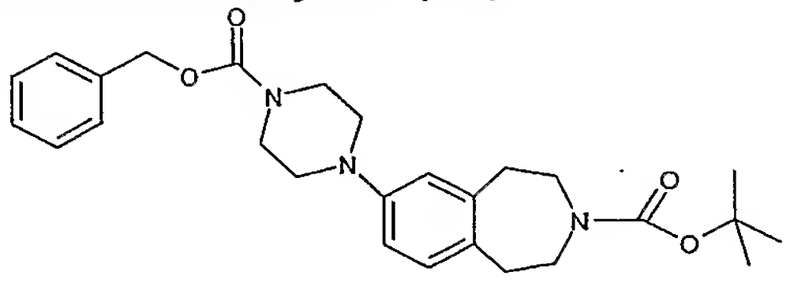
1,1-Dimethylethyl 7-{[(trifluoromethyl)sulfonyl]oxy}-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D1)



Trifluoroacetic anhydride (16ml, 95mmol) was added dropwise over 0.5h to a solution of 1,1-dimethylethyl 7-hydroxy-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (PCT Int. Appl. (2003), 56 pp. CODEN: PIXXD2 WO 2003068752 A1; 25g, 94.93mmol) and triethylamine (20ml, 142mmol) in dry dichloromethane (250ml) at –25°C. The reaction mixture was allowed to warm to room temperature and stirred for 16 hours. Saturated sodium bicarbonate solution (250ml) was cautiously added and the mixture vigorously stirred for 10 minutes. The aqueous phase was separated and re-extracted with dichloromethane (2x100ml). The combined organic extracts were washed with citric acid (3M; 2x200ml), followed by saturated sodium bicarbonate (2x100ml), then brine (200ml) and dried over anhydrous sodium sulfate in the presence of activated charcoal, filtered and evaporated. The crude material was purified by chromatography on silica, eluting with a mixture of ethyl acetate: pentane 1:10 to 1:5 to give the title product MS (ES+) m/e 396 $[M+H]^+$.

Description 2

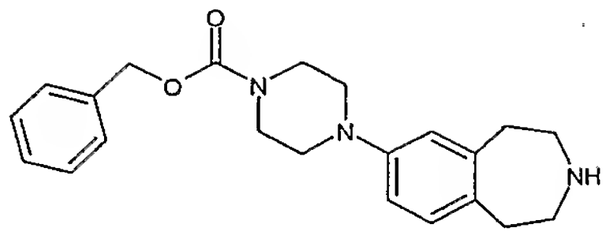
1,1-Dimethylethyl 7-(4-{[(phenylmethyl)oxy]carbonyl}-1-piperazinyl)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D2)



1,1-Dimethylethyl 7-{[(trifluoromethyl)sulfonyl]oxy}-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D1) (36g, 91mmol) was added to a solution of palladium acetate (1.5g, 6.6mmol), *o*-biphenyldi-tert-butylphosphine (4g, 13.6mmol) and potassium phosphate (tribasic; 29g, 136.5mmol) in dry DME (1litre). The mixture was purged with argon for 30 minutes then phenylmethyl 1-piperazinecarboxylate (Aldrich, 45,692-6; 26g, 118mmol) was added and the mixture stirred at 80°C under argon for 5 hours. The mixture was cooled to room temperature and diethyl ether (1 litre) was added. The mixture was filtered through celite and the filtrate evaporated. The residue was purified by chromatography on silica, eluting with a mixture of ethyl acetate: pentane 1:3 to give the title product MS (ES+) m/e 466 $[M+H]^+$.

Description 3

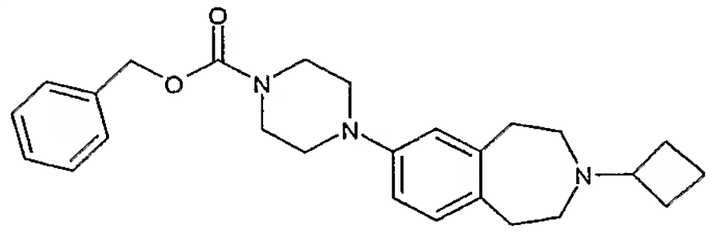
Phenylmethyl 4-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinecarboxylate (D3)



Trifluoroacetic acid (100ml; 1.33mol) was added dropwise over 30 minutes to a solution of 1,1-dimethylethyl 7-(4-{[(phenylmethyl)oxy]carbonyl}-1-piperazinyl)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D2) (24.8g, 53.3mmol) in dichloromethane (300ml) at 0°C under argon. The mixture was stirred for 6 hours, the solvent was then evaporated to dryness and the residue purified by chromatography on silica, eluting with a mixture .880 ammonia: methanol: dichloromethane (1: 9: 90) to afford the title product; MS (ES+) m/e 366 $[M+H]^+$.

Description 4

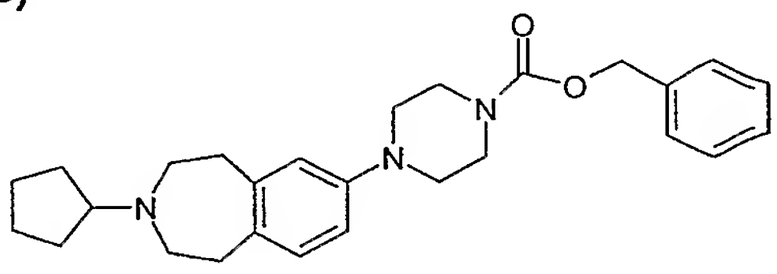
Phenylmethyl 4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinecarboxylate (D4)



Cyclobutanone (287mg, 4.1mmol) was added to a solution of phenylmethyl 4-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinecarboxylate (D3) (1g, 2.7mmol) in dichloromethane (15ml) containing glacial acetic acid (2.5%). The mixture was stirred for 1 hour at room temperature, then sodium triacetoxyborohydride (870mg, 4.1mmol) was added and the mixture stirred at room temperature for 4 hours. The reaction mixture was partitioned between sodium carbonate (2M, 200ml) and dichloromethane (2x200ml). The combined organic extracts were washed with brine (200ml), dried over sodium sulphate, filtered and evaporated. The residue was purified by chromatography on silica, eluting with a mixture .880 ammonia: methanol: dichloromethane (0.5: 4.5: 95) to afford the title product; MS (ES+) m/e 420 $[M+H]^+$.

Description 5

Phenylmethyl 4-(3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinecarboxylate (D5)

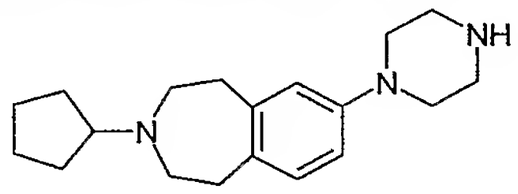


1,1-Dimethylethyl 7-(4-{[(phenylmethyl)oxy]carbonyl}-1-piperazinyl)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D2) (4.2g, 9.1mmol) was dissolved in dichloromethane (10ml) and cooled to 0°C before the slow addition of trifluoroacetic acid (7.0ml, 90mmol). The solution was stirred at room temperature for 3 hours and concentrated *in vacuo*. The crude residue was partitioned between dichloromethane and a 10% sodium bicarbonate

solution (pH = 11). The organic solution was concentrated *in vacuo* and dried for 1 hour (1 mbar, 20°C). To the dry residue dissolved in dichloromethane (50ml), cyclopentanone (1.61ml, 18.2mmol) and acetic acid (0.52ml, 9.1mmol) were added and the solution was stirred for 1 hour before the addition of sodium triacetoxyborohydride (3.86g, 18.2mmol). The reaction was stirred at room temperature for 2 days. A 2N hydrochloric acid aqueous solution (4.5ml, 9.1mmol) was added slowly at 0°C followed by the slow addition of a 3N sodium hydroxide aqueous solution until pH ~ 9. The aqueous phase was extracted 3 times with dichloromethane. The combined extracts were washed with water, brine, dried over magnesium sulfate and concentrated *in vacuo*. The title product was purified by column chromatography eluting with a mixture of dichloromethane:methanol (95:5); MS (ES+) m/e 434 $[M+H]^+$; ^1H NMR ($CDCl_3$) 7.37-7.29 (5H, m), 6.98 (1H, m), 6.69-6.64 (2H, m), 5.16 (2H, s), 3.66-3.63 (4H, m), 3.10 (4H, brs), 2.91-2.85 (5H, m), 2.72-2.70 (4H, brs), 1.86-1.82 (2H, m), 1.67 (2H, m), 1.55-1.45 (4H, m).

Description 6

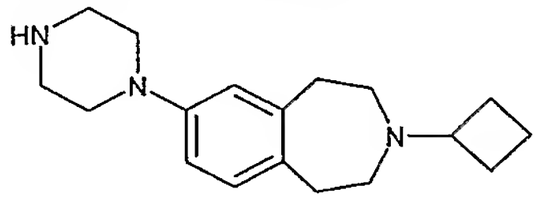
3-Cyclopentyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D6)



Phenylmethyl 4-(3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinecarboxylate (D5) (2.29g, 5.3mmol) was dissolved in a mixture of ethanol:methanol (1:1) (100ml). Palladium (0.5g, 10% on charcoal paste) was added and the reaction mixture was stirred at room temperature under hydrogen (atmospheric pressure) for 12 hours. The mixture was filtered through celite and the filtrate concentrated *in vacuo* and dried overnight (1 mbar, 20°C) to afford the title product; MS (ES+) m/e 300 [M+H]+; ^1H NMR ($CDCl_3$) 6.98 (1H, m), 6.70-6.65 (2H, m), 3.73-3.67 (1H, brs), 3.14-3.11 (4H, m), 3.05-3.03 (4H, m), 2.95-2.91 (5H, m), 2.81-2.78 (4H, brs), 1.91-1.88 (2H, m), 1.71-1.67 (2H, m), 1.58-1.52 (4H, m).

Description 7

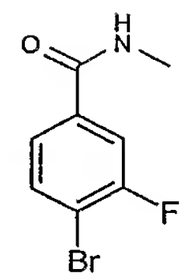
3- Cyclobutyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D7)



The title compound was prepared from phenylmethyl 4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinecarboxylate (D4) using an analogous method to that described for Description 6; MS (ES+) m/e 286 $[M+H]^+$

Description 8

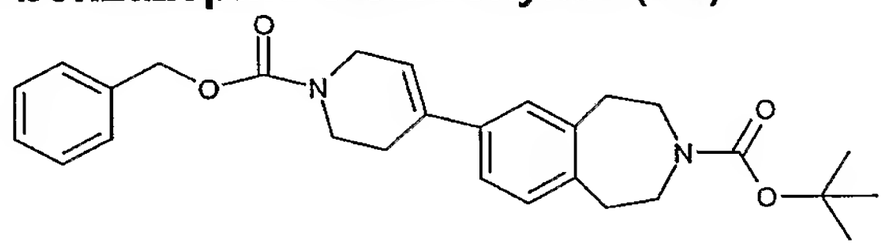
4-Bromo-3-fluoro-N-methylbenzamide (D8)



A mixture of 4-bromo-3-fluorobenzoic acid (470mg, 2.14mmol), methylamine (2M in tetrahydrofuran, 4.3ml, 4.3mmol), polymer bound dicyclohexylcarbodiimide resin (2.5g, 4.3mmol, 1.7mmol/g), 1-hydroxybenzotriazole (580mg, 4.3mmol) and dichloromethane (15ml) were stirred at room temperature for 48 hours. The reaction mixture was filtered and solvent was removed *in vacuo*. The product was dissolved in methanol and applied to a SCX cartridge (Varian bond-elute, 10g) and washed with methanol and then a mixture of 2M ammonia/methanol. The product was purified further by column chromatography eluting 0.5% (2M ammonia in methanol / dichloromethane) to afford the title compound. MS (ES+) m/e 233 $[M+H]^+$.

Description 9

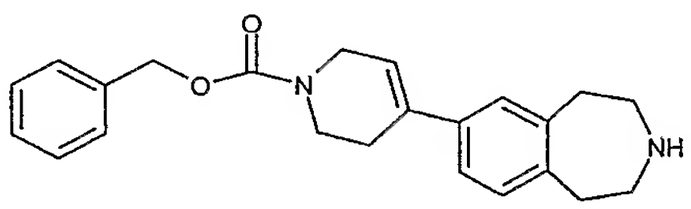
1,1-Dimethylethyl 7-(1-{[(phenylmethyl)oxy]carbonyl}-1,2,3,6-tetrahydro-4-pyridinyl)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D9)



A mixture of phenylmethyl 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-3,6-dihydro-1(2*H*)-pyridinecarboxylate (*Tetrahedron Letters* **41**(2000), 3705) (550mg, 1.6mmol), [1,1'-bis(diphenylphosphino)ferrocene]dichloropalladium(II) (67mg, 10mmol) and potassium carbonate (630mg, 4.6mmol) were suspended in degassed *N*,*N*-dimethylformamide (7 ml). 1,1-dimethylethyl 7-{[(trifluoromethyl)sulfonyl]oxy}-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D1) (PCT Int. Appl. (2002), WO 2002040471 A2) (601mg, 1.5mmol) was then added and the mixture heated at 80°C overnight. The crude mixture was filtered through a pad of celite and washed with ethyl acetate. The filtrate was washed with water, brine, dried over anhydrous magnesium sulfate, filtered and concentrated. The residue was purified by flash chromatography, eluting with a gradient of pentane to 20% ethyl acetate in pentane, to afford the title compound. MS (ES+) m/e 463 $[M+H]^+$.

Description 10

Phenylmethyl 4-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-3,6-dihydro-1(2*H*)-pyridinecarboxylate (D10)

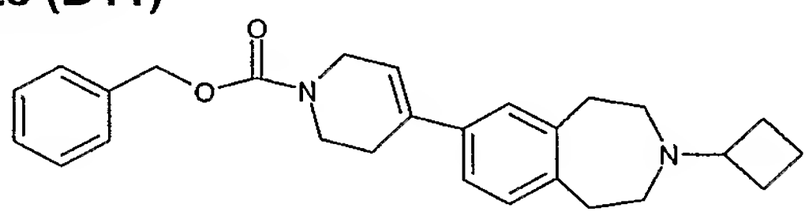


1,1-Dimethylethyl 7-(1-{[(phenylmethyl)oxy]carbonyl}-1,2,3,6-tetrahydro-4-pyridinyl)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D9) (480mg, 0.97mmol) was dissolved in

dichloromethane (3ml) at 0°C and treated with trifluoroacetic acid (3ml). The solution was stirred at room temperature for 1 hour and concentrated *in vacuo*, co-evaporating with dichloromethane. The residue was applied to a SCX cartridge (Varian Bond-elute, 10g) and washed with methanol, then 2M ammonia in methanol. The product containing fractions were concentrated *in vacuo* to a solid that was used in subsequent steps without further purification. MS (ES+) m/e 363 $[M+H]^+$.

Description 11

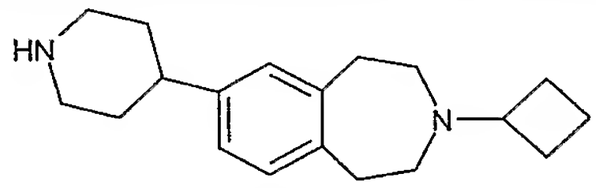
Phenylmethyl 4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-3,6-dihydro-1(2*H*)-pyridinecarboxylate (D11)



A solution of phenylmethyl 4-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-3,6-dihydro-1(2*H*)-pyridinecarboxylate (D10) (280mg, 0.8mmol) and cyclobutanone (0.12ml, 1.5mmol), were stirred at room temperature for 30 minutes in 2.5% acetic acid in methanol. Polystyryl(methyl)trimethylammonium cyanoborohydride (375mg, 4mmol/g loading, 1.5mmol) was added and the solution stirred at room temperature overnight. The reaction mixture was loaded directly on to SCX (Varian Bond-elute, 10g) washing with methanol and eluting product with 2M ammonia in methanol. Product containing fractions were concentrated *in vacuo* and the residue purified by flash chromatography, eluting with a gradient of dichloromethane to 1:9:90 .880 ammonia:ethanol:dichloromethane to give the title compound MS (ES+) m/e 417 $[M+H]^+$.

Description 12

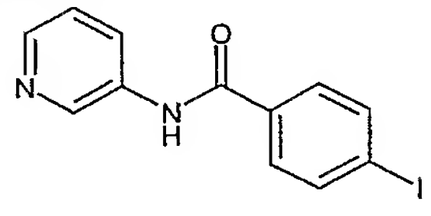
3-Cyclobutyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D12)



A solution of phenylmethyl 4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-3,6-dihydro-1(2*H*)-pyridinecarboxylate (D11) (150mg, 0.36mmol) in ethanol (10ml) was hydrogenated at atmospheric pressure over 10% palladium/charcoal (50mg) for 48 hours. The catalyst was filtered, washed with ethanol and the filtrate concentrated *in vacuo* to afford the title product that was used in the subsequent step without further purification. MS (ES+) m/e 285 $[M+H]^+$.

Description 13

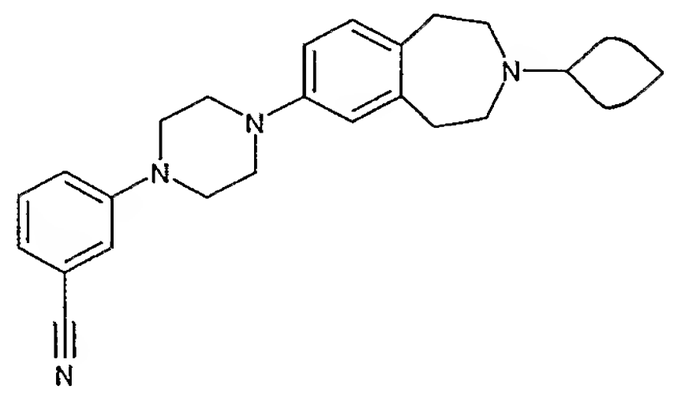
4-Iodo-N-3-pyridinylbenzamide (D13)



3-Aminopyridine (0.12g, 1.3mmol) and triethylamine (0.31ml, 2.3mmol) in dichloromethane (10ml) were cooled to 0°C and treated with 4-iodobenzoyl chloride (0.25g, 0.94mmol). The reaction mixture was stirred at room temperature for 2 hours, after which it was diluted with dichloromethane, washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was triturated in dichloromethane (5ml) and filtered to afford the title compound; MS (ES+), m/e 325 $[M+H]^+$

Example 1

3-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]benzonitrile (E1)



3-Cyclobutyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D7) (111.3mg, 0.39mmol), 3-bromobenzonitrile (70.6mg, 0.39mmol), cesium carbonate (178mg, 0.55mmol), palladium acetate (4mg, 0.018mmol) and (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphane) (15mg, 0.027mmol) were mixed in 2ml of dry toluene. The reaction mixture was heated in microwave at 140°C for 25 minutes. Ethyl acetate was added and the mixture filtered through celite, washed with water and brine, dried over anhydrous sodium sulfate and concentrated *in vacuo*. The crude residue was purified by column chromatography eluting with a mixture of .880 ammonia: methanol: dichloromethane (.5: 4.5: 95) to afford the title product; MS (ES+) m/e 387 $[M+H]^+$.

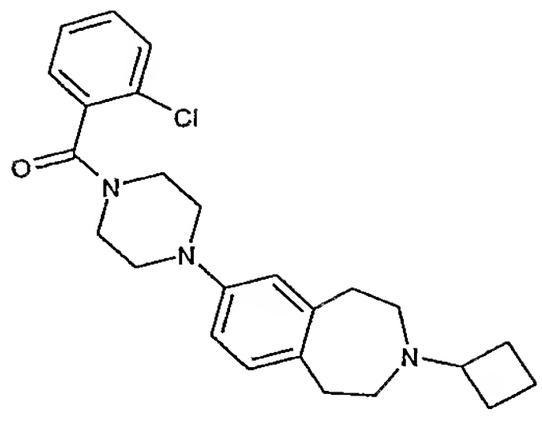
Examples 2 – 3 (E2-3)

Examples 2-3 were prepared from 3-cyclobutyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (D7) and the appropriate benzonitrile using the analogous method to that described for Example 1 (see table)

Example	Benzonitrile	Heating time	LC/MS ($M+H^+$)
4-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-piperazinyl]benzonitrile (E2)	4-bromobenzonitrile	30 mins	387
2-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-piperazinyl]benzonitrile (E3)	2-bromobenzonitrile	100 mins	387

Example 4

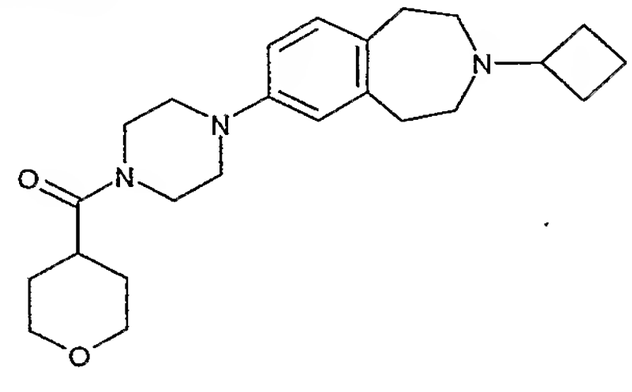
7-{4-[(2-Chlorophenyl)carbonyl]-1-piperazinyl}-3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E4)



A mixture of 2-chlorophenylbenzoic acid (75mg, 0.48mmol), 1*H*-1,2,3-benzotriazol-1-ol (65mg, 0.48mmol) and *N*-cyclohexylcarbodiimide, *N'*-methyl polystyrene (1.8mmol/g) (470mg, 0.8mmol) were stirred at room temperature in dichloromethane for 20 minutes. 3-cyclobutyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (D7) (114mg, 0.4mmol) was added and the mixture stirred at room temperature overnight. The reaction mixture was loaded directly on to a SCX (Varian Bond-elute, 5g) washing with methanol and eluting basic components with 2M ammonia in methanol. The product containing fractions were concentrated *in vacuo* and purified by flash chromatography eluting with a gradient of dichloromethane to 10% 2M ammonia in methanol, to afford the title product. MS (ES+) m/e 424 $[M+H]^+$.

Example 5

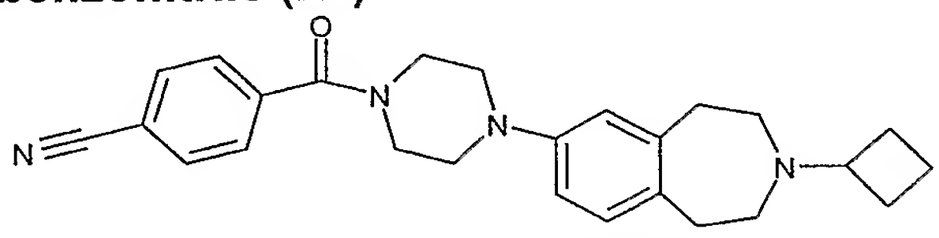
3-Cyclobutyl-7-[4-(tetrahydro-2*H*-pyran-4-ylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E5)



Example 5 was prepared in an analogous manner to Example 4 using tetrahydro-2*H*-pyran-4-carboxylic acid. MS (ES+) m/e 398 $[M+H]^+$.

Example 6

4-{[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]carbonyl}benzonitrile (E6)



A mixture 3- cyclobutyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D7) (57mg, 0.2mmol) and polymer bound triethylamine (3.2mmol/g; 625mg, 2mmol) were suspended in dichloromethane (5ml). The mixture was treated with 4-cyanobenzoyl chloride (80 mg, 0.48mmol) and stirred at room temperature overnight. The resin was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with a

gradient of dichloromethane to 1:9:90 .880 ammonia:ethanol:dichloromethane, to afford the title compound. MS (ES+) m/e 415 $[M+H]^+$.

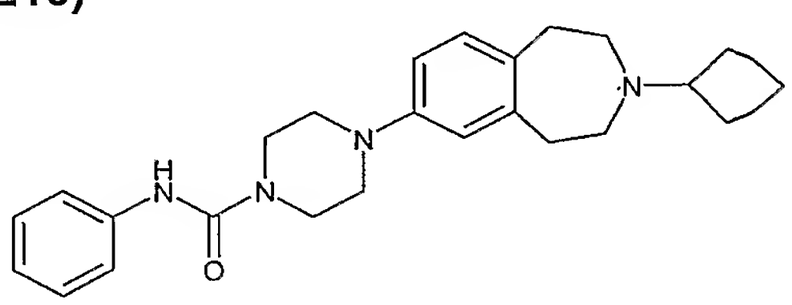
Examples 7-9 (E7-9)

The following examples were prepared in an analogous manner to Example 6 using 3-cyclobutyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (D7) and the appropriate sulfonyl or acid chloride.

Example	Sulfonyl/Acid chloride	LC/MS ($M+H^+$)
7-[4-(2,1,3-Benzoxadiazol-5-ylcarbonyl)-1-piperazinyl]-3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E7)	2,1,3-benzoxadiazole-5-carbonyl chloride	432
7-{4-[(2-Chlorophenyl)sulfonyl]-1-piperazinyl}-3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E8)	2-chlorobenzene sulfonyl chloride	461
3-Cyclobutyl-7-[4-(4-morpholinylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E9)	4-morpholinecarbonyl chloride	399

Example 10

4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-*N*-phenyl-1-piperazinecarboxamide (E10)



In a solution of dry tetrahydrofuran (5ml) and di*iso*propylethylamine (0.2ml, 1.14mmol) cooled at -10°C, triphosgene (67.5mg; 0.23mmol) was added. After 5 minutes stirring at -10°C, a solution of 3-cyclobutyl-7-(1-piperazinyl)-2,3,4,5–tetrahydro-1*H*-3-benzazepine (D7) (130mg, 0.46mmol) in dry tetrahydrofuran (3ml) and di*iso*propylethylamine (0.2ml, 1.14mmol) was added dropwise and stirred at room temperature for 30 minutes. After this time aniline was slowly added with dry tetrahydrofuran (4ml). Reaction mixture was left to stir under argon at room temperature overnight. The mixture was acidified with acetic acid and applied to a SCX ion exchange cartridge (Varian bond–elute, 10g) and washed with methanol followed by a mixture of .880 ammonia: methanol (1: 9). The combined basic fractions were concentrated *in vacuo* and the resulting residue was purified by column chromatography eluting with a mixture of .880 ammonia: methanol: dichloromethane (.25: 2.25: 97.5) to afford the title product; MS (ES+) m/e 405 $[M+H]^+$.

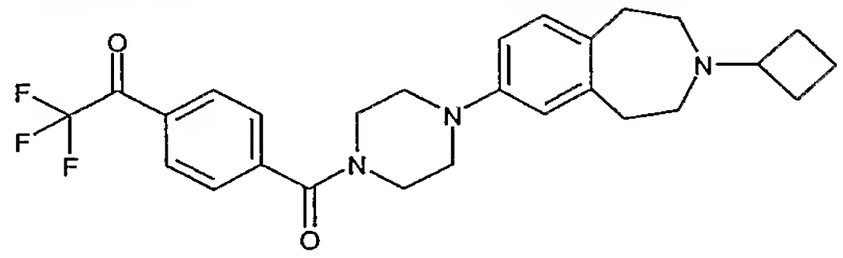
Examples 11-14 (E11-14)

Examples 11-14 were prepared from 3-cyclobutyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (D7) and the appropriate aniline indicated in the table, using an analogous method to that described for Example 10.

Product	Aniline	LC/MS (M+H+)
4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-[4-(methyloxy)phenyl]-1-piperazinecarboxamide (E11)	4-(methyloxy)aniline	435
4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-[3-(methyloxy)phenyl]-1-piperazinecarboxamide (E12)	3-(methyloxy)aniline	435
N-(4-Chlorophenyl)-4-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-piperazinecarboxamide (E13)	4-chloroaniline	439
4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-(4-ethylphenyl)-1-piperazinecarboxamide (E14)	4-ethylaniline	433

Example 15

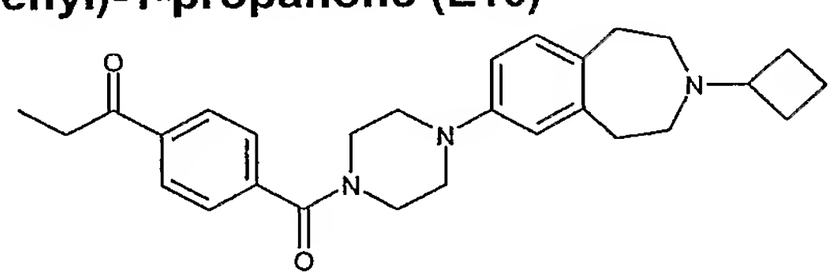
1-(4-{[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]carbonyl}phenyl)-2,2,2-trifluoroethanone (E15)



A mixture of 4-(trifluoroacetyl)benzoic acid (105 mg, 0.48 mmol), *N*-Cyclohexylcarbodiimide *N'*-methyl polystyrene (565mg, 0.96mmol), and 1-hydroxybenzotriazole (129.mg, 0.96mmol) in dry dimethylformamide (5ml) were stirred under argon at room temperature for 30 minutes. A solution of 3-cyclobutyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D7) (114mg, 0.4mmol) in dry dimethylformamide (1ml) was added, and the reaction mixture left to stir at room temperature for one day. The mixture was applied to a SCX ion exchange cartridge (Varian bond-elute, 10g), washed with methanol followed by a mixture of .880 ammonia: methanol (1: 9). The combined basic fractions were concentrated *in vacuo* and the resulting residue purified by column chromatography eluting with a mixture of .880 ammonia: methanol: dichloromethane (.25: 2.25: 97.5) to afford the title product; MS (ES+) m/e 486 $[M+H]^+$.

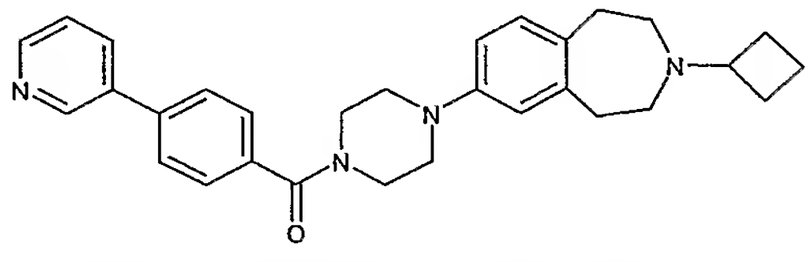
Example 16

1-(4-{[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]carbonyl}phenyl)-1-propanone (E16)



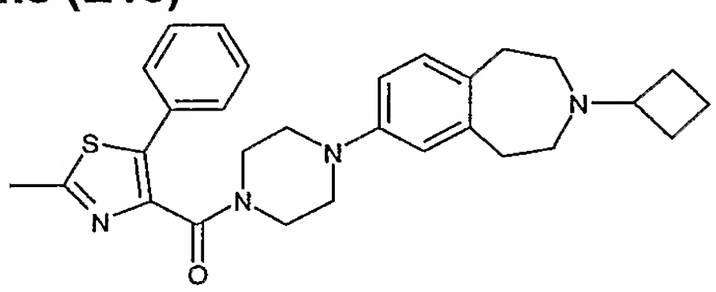
The title compound was prepared from 4-propanoylbenzoic acid and 3-cyclobutyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D7) using the same method described for the preparation of Example 15; MS (ES+) m/e 446 $[M+H]^+$.

Example 17
3-Cyclobutyl-7-(4-{[4-(3-pyridinyl)phenyl]carbonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E17)



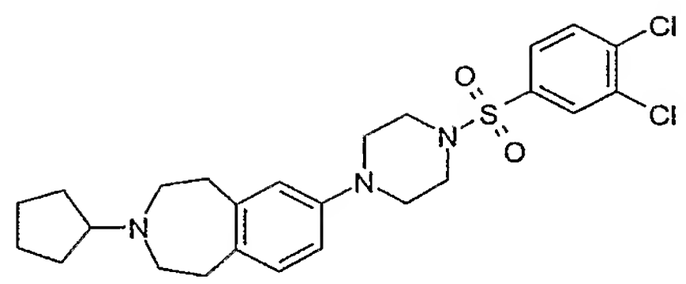
A mixture of *o*-benzotriazol-1-yl-*N*,*N*,*N*',*N*'-tetramethyluroniumhexafluorophosphate (173mg, 0.46mmol) and 4-(3-pyridinyl)benzoic acid (91.6mg, 0.46mmol) in dry dimethylformamide (5ml) was stirred for 30 minutes at room temperature. A solution of 3-cyclobutyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D7) (108.5mg, 0.38mmol) in dry dimethylformamide (5ml) was then added followed by morpholinomethyl polystyrene HL (265mg, 1.14mmol). The reaction mixture was stirred at room temperature under argon overnight, then applied to a SCX ion exchange cartridge (Varian bond-elute, 10g) and washed with methanol followed by a mixture of .880 ammonia: methanol (1: 9). The combined basic fractions were concentrated *in vacuo* and the resulting residue was purified by column chromatography eluting with a mixture of .880 ammonia: methanol: dichloromethane (.5: 4.5: 95) to afford the title product; MS (ES+) m/e 467 $[M+H]^+$.

Example 18
3-Cyclobutyl-7-{4-[(2-methyl-5-phenyl-1,3-thiazol-4-yl)carbonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E18)



The title compound was prepared from 2-methyl-5-phenyl-1,3-thiazole-4-carboxylic acid (U.S. (1966), 5 pp. CODEN: USXXAM US 3282927) and 3-cyclobutyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D7) using the same method described for the preparation of Example 11. MS (ES+) m/e 487 $[M+H]^+$.

Example 19
3-Cyclopentyl-7-{4-[(3,4-dichlorophenyl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E19)



3-Cyclopentyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D6) (0.02g, 0.07mmol) was dissolved in dichloromethane (0.5ml) before 3,4-dichlorobenzenesulfonyl chloride (0.013ml, 0.08mmol) was added followed by morpholinomethyl polystyrene resin (4.3mmol/g, 50.mg, 0.22mmol). The reaction mixture was shaken for 12 hours at room temperature. Scavenging MP-isocyanate resin (3mmol/g, 50mg) and Argopore-Trisamine resin (2.50mmol/g, 50mg) were added and the mixture was shaken for 1 day. Resins were filtered and washed with dichloromethane and the filtrate concentrated *in vacuo* to afford the title compound; MS (ES+) m/e 508 $[M+H]^+$; ^1H NMR ($CDCl_3$) 7.87 (1H, s), 7.64-7.59 (2H, m), 6.98 (1H, d), 6.63-6.60 (2H, m), 3.20 (6H, brs), 2.88 (5H, m), 2.71 (4H, brs), 1.86 (4H, m), 1.68 (2H, m), 1.53 (4H, m).

Examples 20-90

Examples 20-90 (E20-90) were prepared from 3-cyclopentyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (D6) and the appropriate sulfonyl chloride indicated in the table using an analogous method to that described for Example 19 (E19).

Example	Sulfonyl chloride	LC/MS $(M+H)^+$
3-Cyclopentyl-7-[4-(2-thienylsulfonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E20)	2-thiophene sulfonyl chloride	446
4-{[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]sulfonyl}benzonitrile (E21)	4-cyanobenzene sulfonyl chloride	465
3-Cyclopentyl-7-{4-[(4-methyl-3,4-dihydro-2*H*-1,4-benzoxazin-7-yl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E22)	4-methyl-3,4-dihydro-2*H*-1,4-benzoxazine-7-sulfonyl chloride	511
3-Cyclopentyl-7-(4-{[4-(phenyloxy)phenyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E23)	4-(phenyloxy) benzenesulfonyl chloride	532
3-Cyclopentyl-7-[4-(2,3-dihydro-1,4-benzodioxin-6-ylsulfonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E24)	2,3-dihydro-1,4-benzodioxin-6-sulfonyl chloride	498
7-(4-{[3,4-Bis(methyloxy)phenyl]sulfonyl}-1-piperazinyl)-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E25)	3,4-bis(methyloxy) benzenesulfonyl chloride	500

3-Cyclopentyl-7-(4-{[3-(methyloxy)phenyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E26)	3-(methyloxy) benzenesulfonyl chloride	470
3-Cyclopentyl-7-(4-{[4-(methyloxy)phenyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E27)	4-(methyloxy) benzenesulfonyl chloride	470
2,6-Dichloro-4-{[4-(3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]sulfonyl}phenol (E28)	3,5-dichloro-4-hydroxy benzenesulfonyl chloride	525
3-Cyclopentyl-7-[4-(8-quinolinylsulfonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E29)	8-quinoline sulfonyl chloride	491
3-Cyclopentyl-7-[4-(5-isoquinolinylsulfonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E30)	5-isoquinoline sulfonyl chloride	491
3-Cyclopentyl-7-{4-[(1-methyl-1*H*-imidazol-4-yl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E31)	1-methyl-1*H*-imidazole-4-sulfonyl chloride	444
3-Cyclopentyl-7-{4-[(2,4-dimethyl-1,3-thiazol-5-yl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E32)	2,4-dimethyl-1,3-thiazole-5-sulfonyl chloride	475
3-Cyclopentyl-7-{4-[(1,3,5-trimethyl-1*H*-pyrazol-4-yl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E33)	1,3,5-trimethyl-1*H*-pyrazole-4-sulfonyl chloride	472
3-Cyclopentyl-7-[4-(3-thienylsulfonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E34)	3-thiophenesulfonyl chloride	446
7-[4-(1-Benzothien-3-ylsulfonyl)-1-piperazinyl]-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E35)	1-benzothiophene-3-sulfonyl chloride	496
4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-*N*,*N*-dimethyl-1-piperazinesulfonamide (E36)	dimethylsulfamoyl chloride	407
3-Cyclopentyl-7-[4-(thieno[2,3-*b*]pyridin-2-ylsulfonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E37)	thieno[2,3-*b*]pyridine-2-sulfonyl chloride	497
3-Cyclopentyl-7-{4-[(2,2,2-trifluoroethyl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E38)	2,2,2-trifluoroethane sulfonyl chloride	446
3-Cyclopentyl-7-{4-[(phenylmethyl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E39)	Phenylmethane sulfonyl chloride	454
3-Cyclopentyl-7-{4-[(1-methylethyl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine	2-propanesulfonyl chloride	406

(E40)		
3-Cyclopentyl-7-{4-[(4-methylphenyl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E41)	4-methylbenzene sulfonyl chloride	454
7-{4-[(4-Chlorophenyl)sulfonyl]-1-piperazinyl}-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E42)	4-chlorobenzene sulfonyl chloride	475
7-{4-[(2-Chlorophenyl)sulfonyl]-1-piperazinyl}-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E43)	2-chlorobenzene sulfonyl chloride	475
7-{4-[(3-Chlorophenyl)sulfonyl]-1-piperazinyl}-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E44)	3-chlorobenzene sulfonyl chloride	475
3-Cyclopentyl-7-{4-[(2,3-dichlorophenyl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E45)	2,3-dichlorobenzene sulfonyl chloride	509
3-Cyclopentyl-7-(4-{[4-(1,1-dimethylethyl)phenyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E46)	4-(1,1-dimethylethyl) benzenesulfonyl chloride	496
N-(4-{[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]sulfonyl}phenyl)acetamide (E47)	4-(acetylamino) benzenesulfonyl chloride	497
1-(4-{[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]sulfonyl}phenyl)ethanone (E48)	4-acetylbenzene sulfonyl chloride	482
3-Cyclopentyl-7-(4-{[2-(1-naphthalenyl)ethyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E49)	2-(1-naphthalenyl) ethanesulfonyl chloride	518
4-{[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]sulfonyl}benzoic acid (E50)	4-(chlorosulfonyl) benzoic acid	484
3-Cyclopentyl-7-(4-{[4-(trifluoromethyl)phenyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E51)	4-(trifluoromethyl) benzenesulfonyl chloride	508
7-[4-(4-Biphenylylsulfonyl)-1-piperazinyl]-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E52)	4-biphenylsulfonyl chloride	516
3-Cyclopentyl-7-(4-{[5-(1,3-oxazol-5-yl)-2-thienyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E53)	5-(1,3-oxazol-5-yl)-2-thiophenesulfonyl chloride	513
3-Cyclopentyl-7-[4-(2-naphthalenylsulfonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine	2-naphthalene sulfonyl chloride	490

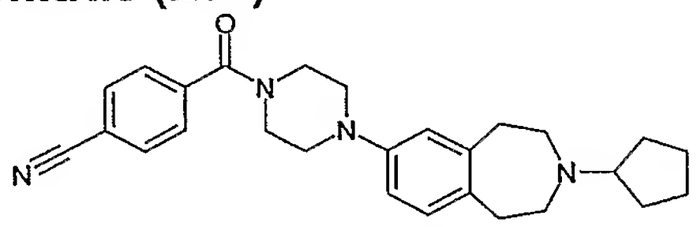
(E54)		
5-{[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]sulfonyl}-*N*,*N*-dimethyl-1-naphthalenamine (E55)	5-(dimethylamino)-1-naphthalene sulfonyl chloride	533
3-Cyclopentyl-7-(4-{[(*E*)-2-phenylethenyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E56)	(*E*)-2-phenylethene sulfonyl chloride	466
3-Cyclopentyl-7-(4-{[4-(1-methylethyl)phenyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E57)	4-(1-methylethyl) benzenesulfonyl chloride	482
7-{4-[(3-Chloro-2-methylphenyl)sulfonyl]-1-piperazinyl}-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E58)	3-chloro-2-methylbenzene sulfonyl chloride	489
3-Cyclopentyl-7-[4-(1-naphthalenylsulfonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E59)	1-naphthalene sulfonyl chloride	490
7-{4-[(5-Chloro-2-thienyl)sulfonyl]-1-piperazinyl}-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E60)	5-chloro-2-thiophenesulfonyl chloride	481
3-Cyclopentyl-7-[4-(methylsulfonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E61)	methanesulfonyl chloride	378
3-Cyclopentyl-7-(4-{[3-(trifluoromethyl)phenyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E62)	3-(trifluoromethyl) benzenesulfonyl chloride	508
3-Cyclopentyl-7-(4-{[5-(2-pyridinyl)-2-thienyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E63)	5-(2-pyridinyl)-2-thiophenesulfonyl chloride	523
7-{4-[(4-Chloro-1-benzothien-2-yl)sulfonyl]-1-piperazinyl}-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E64)	4-chloro-1-benzothiophene-2-sulfonyl chloride	531
7-[4-(2,1,3-Benzoxadiazol-4-ylsulfonyl)-1-piperazinyl]-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E65)	2,1,3-benzoxadiazole-4-sulfonyl chloride	482
3-Cyclopentyl-7-{4-[(1,2-dimethyl-1*H*-imidazol-4-yl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E66)	1,2-dimethyl-1*H*-imidazole-4-sulfonyl chloride	458
N-(5-{[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]sulfonyl}-4-methyl-1,3-thiazol-2-yl)acetamide (E67)	2-(acetylamino)-4-methyl-1,3-thiazole-5-sulfonyl chloride	518
3-Cyclopentyl-7-{4-[(3,5-dichlorophenyl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E68)	3,5-dichlorobenzene sulfonyl chloride	509

3-Cyclopentyl-7-[4-({4-[(trifluoromethyl)oxy]phenyl}sulfonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E69)	4-[(trifluoromethyl) oxy]benzene sulfonyl chloride	524
3-Cyclopentyl-7-(4-{[2-(trifluoromethyl)phenyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E70)	2-(trifluoromethyl) benzenesulfonyl chloride	508
3-Cyclopentyl-7-{4-[(3,5-dimethyl-4-isoxazolyl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E71)	3,5-dimethyl-4-isoxazolesulfonyl chloride	459
3-Cyclopentyl-7-(4-{[6-(phenyloxy)-3-pyridinyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E72)	6-(phenyloxy)-3-pyridinesulfonyl chloride	533
3-Cyclopentyl-7-[4-(phenylsulfonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E73)	benzenesulfonyl chloride	440
3-Cyclopentyl-7-{4-[(5-methyl-1-phenyl-1*H*-pyrazol-4-yl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E74)	5-methyl-1-phenyl-1*H*-pyrazole-4-sulfonyl chloride	520
7-(4-{[(4-Chlorophenyl)methyl]sulfonyl}-1-piperazinyl)-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E75)	(4-chlorophenyl) methanesulfonyl chloride	489
3-Cyclopentyl-7-[4-({[4-(trifluoromethyl)phenyl]methyl}sulfonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E76)	[4-(trifluoromethyl) phenyl]methane sulfonyl chloride	522
3-Cyclopentyl-7-[4-(2,3-dihydro-1-benzofuran-5-ylsulfonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E77)	2,3-dihydro-1-benzofuran-5-sulfonyl chloride	482
6-{[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]sulfonyl}-2*H*-chromen-2-one (E78)	2-oxo-2*H*-chromene-6-sulfonyl chloride	508
3-Cyclopentyl-7-(4-{[5-(3-isoxazolyl)-2-thienyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E79)	5-(3-isoxazolyl)-2-thiophenesulfonyl chloride	513
7-[4-(2,1,3-Benzothiadiazol-5-ylsulfonyl)-1-piperazinyl]-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E80)	2,1,3-benzothiadiazole-5-sulfonyl chloride	498
7-(4-{[5-Chloro-2-(methyloxy)phenyl]sulfonyl}-1-piperazinyl)-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E81)	5-chloro-2-(methyloxy) benzenesulfonyl chloride	505
3-Cyclopentyl-7-{4-[(5-fluoro-2-methylphenyl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E82)	5-fluoro-2-methylbenzene sulfonyl chloride	472

7-{4-[(4-Bromo-2-ethylphenyl)sulfonyl]-1-piperazinyl}-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E83)	4-bromo-2-ethylbenzene sulfonyl chloride	547
7-{4-[(6-Chloroimidazo[2,1-*b*][1,3]thiazol-5-yl)sulfonyl]-1-piperazinyl}-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E84)	6-chloroimidazo[2,1-*b*][1,3]thiazole-5-sulfonyl chloride	521
3-Cyclopentyl-7-(4-{[3-(5-methyl-1,3,4-oxadiazol-2-yl)phenyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E85)	3-(5-methyl-1,3,4-oxadiazol-2-yl)benzenesulfonyl chloride	522
3-Cyclopentyl-7-{4-[(2,5-dimethyl-3-thienyl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E86)	2,5-dimethyl-3-thiophenesulfonyl chloride	474
3-Cyclopentyl-7-(4-{[4-methyl-2-(methyloxy)phenyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E87)	4-methyl-2-(methyloxy) benzenesulfonyl chloride	484
3-Cyclopentyl-7-(4-{[2-(3-methylphenyl)ethyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E88)	2-(3-methylphenyl) ethanesulfonyl chloride	482
3-Cyclopentyl-7-(4-{[4-(methylsulfonyl)phenyl]sulfonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E89)	4-(methylsulfonyl) benzenesulfonyl chloride	518
3-Cyclopentyl-7-{4-[(3,4,5-trimethylphenyl)sulfonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E90)	3,4,5-trimethylbenzene sulfonyl chloride	482

Example 91

4-{[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]carbonyl}benzonitrile (E91)



To a solution of 4-cyanobenzoic acid (18mg, 0.07mmol) in dichloromethane (2ml) *O*-Benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium hexafluorophosphate (22.7mg, 0.06mmol) was added. The reaction was stirred for 40 minutes before the addition of 3-cyclopentyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D6) (14.9mg, 0.05 mmol) followed by morpholinomethyl-polystyrene resin (4.3mmol/g, 34.8mg, 0.15mmol). The reaction mixture was shaken at room temperature for 12 hours. MP-carbonate resin (2.8mmol/g, 0.18g, 0.5mmol) was added and the reaction was shaken for 1 day. The resin was filtered and

washed 3 times with dichloromethane and the filtrate solutions were drained onto a SCX ion-exchange cartridge (Varian bond-elute, 500 mg). The cartridge was washed with methanol then 2M ammonia in methanol solution. Solvents were removed *in vacuo* and the crude residue was purified by column chromatography eluting with dichloromethane then ethyl acetate, then methanol to afford the title product (E91); MS (ES+) m/e 429 $[M+H]^+$; ^1H NMR ($CDCl_3$) 7.73 (2H, d), 7.54 (2H, d), 7.01 (1H, d), 6.70-6.65 (2H, m), 3.92 (2H, brs), 3.62-3.47 (2H, m), 3.22-3.08 (4H, m), 2.91 (5H, m), 2.72 (4H, m), 1.87 (2H, m), 1.67 (2H,.m), 1.56-1.47 (4H, m).

Examples 92-190 (E92-190)

Examples 92-190 (E92-E190) were prepared using an analogous method to that described for Example 91 (E91) from 3-cyclopentyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D6) and the appropriate carboxylic acid as indicated in the table. No further purification was required in Examples 161-190 (E161-E190) after recovery of the title compound from the SCX ion-exchange cartridge. Secondary purification was performed by column chromatography eluting with dichloromethane then ethyl acetate, then methanol for Examples 92-93 (E92-E93), or by Mass Spectrometer-coupled High Performance Liquid Chromatography (SUPELCOSIL™ ABZ+PLUS 12μM column, eluents: acetonitrile:water + 0.1% v/v trifluoroacetic acid) for Examples 94-160 (E95-E160).

Example	Acid	LC/MS $(M+H)^+$
3-Cyclopentyl-7-[4-(4-pyridinylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E92)	4-pyridinecarboxylic acid	405
3-Cyclopentyl-7-[4-(cyclopentylcarbonyl)-1-piperazinyl]–2,3,4,5-tetrahydro-1*H*-3-benzazepine (E93)	Cyclopentane carboxylic acid	396
3-Cyclopentyl-7-[4-(1*H*-indol-3-ylcarbonyl)-1-piperazinyl]–2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E94)	1*H*-indole-3-carboxylic acid	557
3-Cyclopentyl-7-(4-{[2-(phenyloxy)phenyl]carbonyl}-1-piperazinyl)–2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E95)	2-(phenyloxy)benzoic acid	610
3-Cyclopentyl-7-(4-{[2-(methyloxy)phenyl]carbonyl}-1-piperazinyl)–2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E96)	2-(methyloxy)benzoic acid	548
3-Cyclopentyl-7-{4-[(3,4-dichlorophenyl)carbonyl]-1-piperazinyl}–2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E97)	3,4-dichlorobenzoic acid	587
3-Cyclopentyl-7-[4-(2-phenylpropanoyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate	2-phenylpropanoic acid	546

salt (E98)		
3-Cyclopentyl-7-(4-{[4-(1*H*-pyrazol-1-yl)phenyl]acetyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E99)	[4-(1*H*-pyrazol-1-yl)phenyl]acetic acid	598
3-Cyclopentyl-7-{4-[(4-methyl-2-phenyl-3-furanyl)carbonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E100)	4-methyl-2-phenyl-3-furancarboxylic acid	598
3-Cyclopentyl-7-(4-{[4-(1,1-dimethylethyl)phenyl]carbonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E101)	4-(1,1-dimethylethyl) benzoic acid	574
(3-{[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]carbonyl}phenyl)(phenyl)methanone trifluoroacetate salt (E102)	3-(phenylcarbonyl) benzoic acid	622
3-Cyclopentyl-7-[4-(2,3-dihydro-1-benzofuran-2-ylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E103)	2,3-dihydro-1-benzofuran-2-carboxylic acid	560
7-[4-(4-Biphenylylcarbonyl)-1-piperazinyl]-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E104)	4-biphenylcarboxylic acid	594
7-{4-[(5-Chloro-1-benzothien-2-yl)carbonyl]-1-piperazinyl}-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E105)	5-chloro-1-benzothiophene-2-carboxylic acid	609
7-[4-(1-Benzothien-2-ylcarbonyl)-1-piperazinyl]-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E106)	1-benzothiophene-2-carboxylic acid	574
3-Cyclopentyl-7-{4-[(5-methyl-4-phenyl-2-thienyl)carbonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E107)	5-methyl-4-phenyl-2-thiophenecarboxylic acid	614
7-[4-(1,3-Benzothiazol-6-ylcarbonyl)-1-piperazinyl]-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E108)	1,3-benzothiazole-6-carboxylic acid	575
3-Cyclopentyl-7-[4-(phenylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E109)	benzoic acid	518
3-Cyclopentyl-7-[4-(2-naphthalenylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E110)	2-naphthalene carboxylic acid	568
1-(4-{[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]carbonyl}phenyl) ethanone trifluoroacetate salt (E111)	4-acetylbenzoic acid	560

3-Cyclopentyl-7-(4-{[4-(1-methylethyl)phenyl]carbonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E112)	4-(1-methylethyl)benzoic acid	560
3-Cyclopentyl-7-(4-{[4-(trifluoromethyl)phenyl]carbonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E113)	4-(trifluoromethyl) benzoic acid	586
3-Cyclopentyl-7-[4-({3-[(trifluoromethyl)oxy]phenyl}carbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E114)	3-[(trifluoromethyl)oxy] benzoic acid	602
7-(4-{[2-Bromo-5-(methyloxy)phenyl]carbonyl}-1-piperazinyl)-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E115)	2-bromo-5-(methyloxy)benzoic acid	627
N-{2-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]-2-oxoethyl}-2-methylbenzamide trifluoroacetate salt (E116)	*N*-[(2-methylphenyl) carbonyl]glycine	589
3-Cyclopentyl-7-[4-(1,3-dihydro-2*H*-isoindol-2-ylacetyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E117)	1,3-dihydro-2*H*-isoindol-2-ylacetic acid	573
7-{4-[(3-Chlorophenyl)carbonyl]-1-piperazinyl}-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E118)	3-chlorobenzoic acid	553
7-{4-[(4-Chlorophenyl)carbonyl]-1-piperazinyl}-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E119)	4-chlorobenzoic acid	553
7-{4-[(2-Chlorophenyl)carbonyl]-1-piperazinyl}-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E120)	2-chlorobenzoic acid	553
3-Cyclopentyl-7-{4-[(4-nitrophenyl)carbonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E121)	4-nitrobenzoic acid	563
N-(4-{[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]carbonyl}phenyl)acetamide trifluoroacetate salt (E122)	4-(acetylamino) benzoic acid	575
(4-{[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]carbonyl}phenyl)dimethylamine trifluoroacetate salt (E123)	4-(dimethylamino) benzoic acid	561

3-Cyclopentyl-7-(4-{[3-(methyloxy)phenyl]carbonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E124)	3-(methyloxy) benzoic acid	548
3-Cyclopentyl-7-[4-({4-[(1-methylethyl)oxy]phenyl}carbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E125)	4-[(1-methylethyl)oxy] benzoic acid	576
3-Cyclopentyl-7-(4-{[4-(methyloxy)phenyl]carbonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E126)	4-(methyloxy)benzoic acid	548
7-(4-{[3-Chloro-5-(methyloxy)phenyl]carbonyl}-1-piperazinyl)-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E127)	3-chloro-5-(methyloxy)benzoic acid	583
7-[4-(1,3-Benzodioxol-5-ylacetyl)-1-piperazinyl]-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E128)	1,3-benzodioxol-5-ylacetic acid	576
3-Cyclopentyl-7-(4-{[5-(phenylmethyl)-2-furanyl]carbonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E129)	5-(phenylmethyl)-2-furancarboxylic acid	598
3-Cyclopentyl-7-[4-(3-furanylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E130)	3-furancarboxylic acid	508
3-Cyclopentyl-7-(4-{[3-(2-furanyl)phenyl]carbonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E131)	3-(2-furanyl)benzoic acid	584
3-Cyclopentyl-7-[4-(cyclopropylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E132)	Cyclopropane carboxylic acid	482
3-Cyclopentyl-7-[4-(3,3-dimethylbutanoyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E133)	3,3-dimethylbutanoic acid	512
3-Cyclopentyl-7-{4-[(2*E*)-3-phenyl-2-propenoyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E134)	(2*E*)-3-phenyl-2-propenoic acid	544
3-Cyclopentyl-7-[4-({*cis*-4-[(1,1-dimethylethyl)oxy]cyclohexyl}carbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E135)	*cis*-4-[(1,1-dimethylethyl)oxy] cyclohexane carboxylic acid	596
3-Cyclopentyl-7-(4-{[1-(1-methylethyl)-4-piperidinyl]carbonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E136)	1-(1-methylethyl)-4-piperidinecarboxylic acid	567

1-{2-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]-2-oxoethyl}-2-piperidinone trifluoroacetate salt (E137)	(2-oxo-1-piperidinyl)acetic acid	553
3-Cyclopentyl-7-(4-{[(1-methylethyl)oxy]acetyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E138)	[(1-methylethyl)oxy] acetic acid	514
N-{(1*R*)-2-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]-2-oxo-1-phenylethyl}acetamide trifluoroacetate salt (E139)	(2*R*)-(acetylamino) (phenyl)ethanoic acid	589
3-Cyclopentyl-7-{4-[1-(phenylmethyl)-L-prolyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E140)	1-(phenylmethyl)-L-proline	601
3-Cyclopentyl-7-[4-(2,3-dihydro-1*H*-inden-2-ylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E141)	2,3-dihydro-1*H*-indene-2-carboxylic acid	558
3-Cyclopentyl-7-{4-[3-methyl-2-(phenylmethyl)butanoyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E142)	3-methyl-2-(phenylmethyl) butanoic acid	588
3-Cyclopentyl-7-{4-[(1,1-dioxido-3,4-dihydro-2*H*-1-benzothiopyran-6-yl)carbonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E143)	3,4-dihydro-2*H*-1-benzothiopyran-6-carboxylic acid 1,1-dioxide	622
3-Cyclopentyl-7-(4-{[4-(methylsulfonyl)phenyl]carbonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E144)	4-(methylsulfonyl) benzoic acid	596
3-Cyclopentyl-7-[4-(3,4-dihydro-2*H*-chromen-2-ylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E145)	3,4-dihydro-2*H*-chromene-2-carboxylic acid	574
3-Cyclopentyl-7-[4-(2,3-dihydro-1-benzofuran-7-ylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E146)	2,3-dihydro-1-benzofuran-7-carboxylic acid	560
3-Cyclopentyl-7-(4-{[4-(3-pyridinyl)phenyl]carbonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E147)	4-(3-pyridinyl)benzoic acid	595
3-Cyclopentyl-7-[4-(3-quinolinylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E148)	3-quinolinecarboxylic acid	569
3-Cyclopentyl-7-[4-(pyrazolo[1,5-*a*]pyridin-3-ylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E149)	pyrazolo[1,5-*a*]pyridine-3-carboxylic acid	558

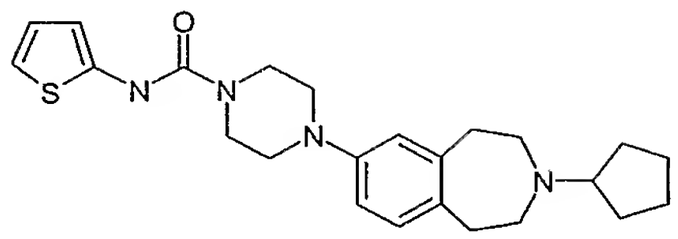
3-Cyclopentyl-7-[4-(5-isoquinolinylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E150)	5-isoquinoline carboxylic acid	569
7-[4-(1-Benzothien-3-ylcarbonyl)-1-piperazinyl]-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E151)	1-benzothiophene-3-carboxylic acid	574
3-Cyclopentyl-7-(4-{[5-(2-pyridinyl)-2-thienyl]carbonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E152)	5-(2-pyridinyl)-2-thiophenecarboxylic acid	601
3-Cyclopentyl-7-{4-[(1,3-dimethyl-1*H*-thieno[2,3-*c*]pyrazol-5-yl)carbonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E153)	1,3-dimethyl-1*H*-thieno[2,3-*c*]pyrazole-5-carboxylic acid	592
3-Cyclopentyl-7-{4-[(4-methyl-2-phenyl-1,3-thiazol-5-yl)acetyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E154)	(4-methyl-2-phenyl-1,3-thiazol-5-yl)acetic acid	629
7-[4-(1,3-Benzothiazol-2-ylcarbonyl)-1-piperazinyl]-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E155)	1,3-benzothiazole-2-carboxylic acid	575
3-Cyclopentyl-7-[4-(imidazo[2,1-*b*][1,3]thiazol-5-ylacetyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E156)	imidazo[2,1-*b*][1,3]thiazol-5-ylacetic acid	578
3-Cyclopentyl-7-(4-{[4-(3,5-dimethyl-1*H*-pyrazol-1-yl)phenyl]carbonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E157)	4-(3,5-dimethyl-1*H*-pyrazol-1-yl)benzoic acid	612
3-Cyclopentyl-7-{4-[(2,4-dimethyl-1,3-oxazol-5-yl)carbonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E158)	2,4-dimethyl-1,3-oxazole-5-carboxylic acid	537
3-Cyclopentyl-7-[4-(4-pyridinylacetyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine trifluoroacetate salt (E159)	4-pyridinylacetic acid	533
6-{2-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinyl]-2-oxoethyl}-2(1*H*)-quinolinone trifluoroacetate salt (E160)	(2-oxo-1,2-dihydro-6-quinolinyl)acetic acid	599
3-Cyclopentyl-7-[4-(phenylacetyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E161)	phenylacetic acid	418
3-Cyclopentyl-7-(4-{[4-(1-methylethyl)phenyl]acetyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E162)	[4-(1-methylethyl)phenyl] acetic acid	460
3-Cyclopentyl-7-[4-(2-naphthalenylacetyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E163)	2-naphthalenylacetic acid	468

3-Cyclopentyl-7-[4-(diphenylacetyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E164)	diphenylacetic acid	494
3-Cyclopentyl-7-(4-{[4-(trifluoromethyl)phenyl]acetyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E165)	[4-(trifluoromethyl) phenyl]acetic acid	486
7-{4-[(4-Chlorophenyl)acetyl]-1-piperazinyl}-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E166)	(4-chlorophenyl) acetic acid	453
3-Cyclopentyl-7-(4-{[4-(methyloxy)phenyl]acetyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E167)	[4-(methyloxy)phenyl] acetic acid	448
3-Cyclopentyl-7-[4-(3-thienylacetyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E168)	3-thienylacetic acid	424
7-[4-(1-Benzothien-4-ylacetyl)-1-piperazinyl]-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E169)	1-benzothien-4-ylacetic acid	474
3-Cyclopentyl-7-(4-{[4-(1-piperidinylcarbonyl)phenyl]carbonyl}-1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E170)	4-(1-piperidinylcarbonyl) benzoic acid	515
7-[4-(1-Benzofuran-4-ylcarbonyl)-1-piperazinyl]-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E171)	1-benzofuran-4-carboxylic acid	444
3-Cyclopentyl-7-[4-(2-furanylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E172)	2-furancarboxylic acid	394
3-Cyclopentyl-7-{4-[(2,5-dimethyl-3-furanyl)carbonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E173)	2,5-dimethyl-3-furancarboxylic acid	422
3-Cyclopentyl-7-[4-(1-methyl-L-prolyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E174)	1-methyl-L-proline	411
3-Cyclopentyl-7-{4-[(phenyloxy)acetyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E175)	(phenyloxy)acetic acid	434
3-Cyclopentyl-7-[4-(2-thienylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E176)	2-thiophenecarboxylic acid	410
3-Cyclopentyl-7-[4-(3-thienylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E177)	3-thiophenecarboxylic acid	410
3-Cyclopentyl-7-{4-[(2,4-dimethyl-1,3-thiazol-5-yl)acetyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E178)	(2,4-dimethyl-1,3-thiazol-5-yl)acetic acid	453

3-Cyclopentyl-7-[4-(1,3-thiazol-5-ylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E179)	1-(1,3-thiazol-5-yl)ethanone	411
3-Cyclopentyl-7-{4-[(5-phenyl-1,3-thiazol-4-yl)carbonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E180)	5-phenyl-1,3-thiazole–4-carboxylic acid	487
3-Cyclopentyl-7-[4-(1,3-thiazol-4-ylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E181)	1,3-thiazole-4-carboxylic acid	411
3-Cyclopentyl-7-[4-(pyrazolo[1,5-*a*]pyrimidin-3-ylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E182)	pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid	445
3-Cyclopentyl-7-{4-[(1-methyl-1*H*-indazol-3-yl)carbonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E183)	1-methyl-1*H*-indazole-3-carboxylic acid	458
7-[4-(2,1,3-Benzoxadiazol-5-ylcarbonyl)-1-piperazinyl]-3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E184)	2,1,3-benzoxadiazole-5-carboxylic acid	446
3-Cyclopentyl-7-{4-[(1-methyl-1*H*-pyrazol-5-yl)carbonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E185)	1-methyl-1*H*-pyrazole-5-carboxylic acid	408
3-Cyclopentyl-7-{4-[(1-methyl-3-phenyl-1*H*-pyrazol-4-yl)carbonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E186)	1-methyl-3-phenyl-1*H*-pyrazole-4-carboxylic acid	484
3-Cyclopentyl-7-{4-[(3,5-dimethyl-4-isoxazolyl)carbonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E187)	3,5-dimethyl-4-isoxazolecarboxylic acid	423
3-Cyclopentyl-7-{4-[(4-methyl-1,2,5-oxadiazol-3-yl)acetyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E188)	(4-methyl-1,2,5-oxadiazol-3-yl)acetic acid	424
3-Cyclopentyl-7-{4-[(1-methyl-1*H*-imidazol-2-yl)acetyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E189)	(1-methyl-1*H*-imidazol-2-yl)acetic acid	422
3-Cyclopentyl-7-{4-[(1-methyl-1*H*-imidazol-2-yl)carbonyl]-1-piperazinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E190)	1-methyl-1*H*-imidazole-2-carboxylic acid	408

Example 191

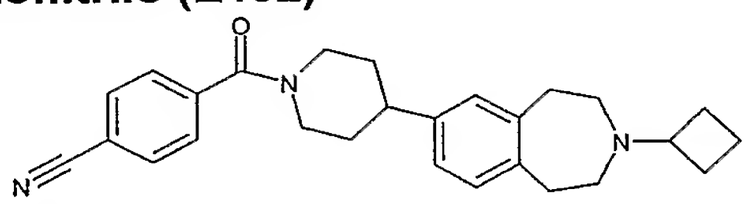
4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-*N*-2–thienyl-1-piperazinecarboxamide (E191)



3-Cyclopentyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D6) (12mg, 0.04mmol) was dissolved in dry dichloromethane (0.5ml) under argon and 2-isocyanatothiophene (6mg, 0.05mmol) was added. The solution was stirred at room temperature for 12 hours. Argopore-trisamine resin (4.17mmol/g, 0.1g, 0.4mmol) was added and the reaction mixture stirred for 12 hours. Resin was filtered and washed several times with dichloromethane and the filtrate concentrated *in vacuo* to afford the title compound; MS (ES+) m/e 425 $[M+H]^+$; ^1H NMR ($CDCl_3$) 7.25 (1H, s), 7.01 (1H, d), 6.99-6.79 (2H, m), 6.70-6.65 (2H, m), 6.57-6.55 (1H, d), 3.65-3.63 (4H, m), 3.19-3.16 (4H, m), 2.90-2.82 (5H, m), 2.70-2.66 (4H, m), 1.86-1.83 (2H, m), 1.68-1.65 (2H,.m), 1.55-1.45 (4H, m).

Example 192

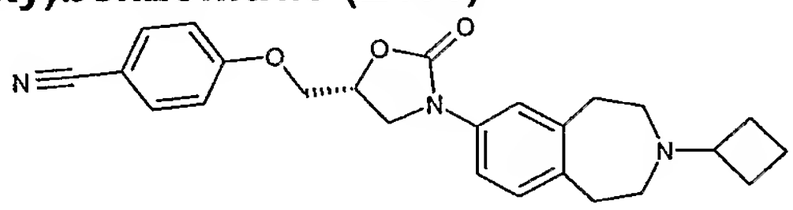
4-{[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]carbonyl}benzonitrile (E192)



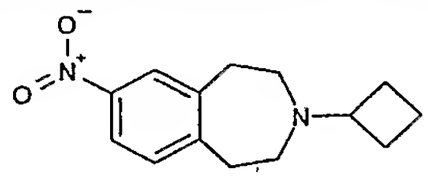
A mixture of 3-cyclobutyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D12) (100mg, 0.35mmol) and polymer bound triethylamine (547mg, 1.75mmol) were suspended in dichloromethane (5ml). The mixture was treated with 4-cyanobenzoyl chloride (70mg, 0.42mmol) and stirred at room temperature overnight. The resin was filtered and the filtrate concentrated *in vacuo*. The residue was purified by flash chromatography, eluting with a gradient of dichloromethane to 1:9:90 .880 ammonia:ethanol:dichloromethane, to afford the title compound. MS (ES+) m/e 414 $[M+H]^+$.

Example 193

4-({[(5*R*)-3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-2-oxo-1,3-oxazolidin-5-yl]methyl}oxy)benzonitrile (E193)



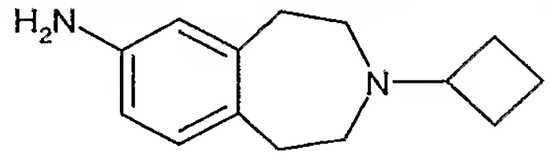
Step 1: 3-Cyclobutyl-7-nitro-2,3,4,5-tetrahydro-1*H*-3-benzazepine



A solution of 7-nitro-2,3,4,5-tetrahydro-1*H*-3-benzazepine (WO 03/068752) (5.8g, 30.2mmol) in dry dichloromethane (200ml) was treated with cyclobutanone (3.4ml) and sodium triacetoxyborohydride and stirred at ambient temperature for 1 hour. Saturated

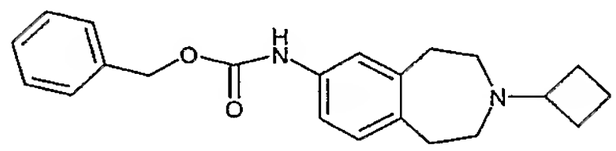
sodium hydrogen carbonate solution and dichloromethane were added and the layers separated. The organic layer was washed with saturated sodium hydrogen carbonate solution, water and saturated brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. MS (ES+) m/e 247 $[M+H]^+$.

Step 2: 3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-amine



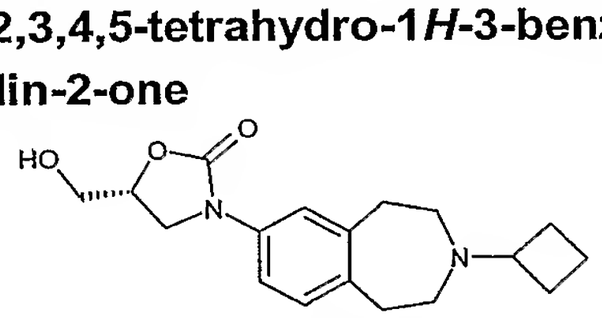
A solution of 3-cyclobutyl-7-nitro-2,3,4,5-tetrahydro-1*H*-3-benzazepine (product of E193, step 1) (6.8g, 27.6mmol) in methanol (60ml) and tetrahydrofuran (90ml) was hydrogenated overnight in the presence of 10% palladium on carbon paste. After filtration of the catalyst through Kieselguhr, the filtrate was concentrated *in vacuo* to afford the title compound. MS (ES+) m/e 217 $[M+H]^+$.

Step 3: Phenylmethyl (3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)carbamate



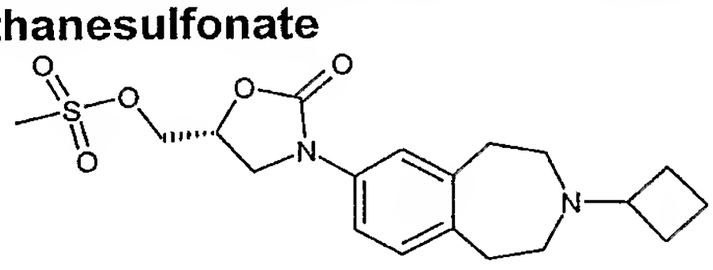
A solution of 3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-amine (product of E193, step 2) (1.0g, 4.6mmol) in acetone (20ml) and water (5ml) was treated with sodium hydrogen carbonate (1.1g, 12.7mmol) and benzyl chloroformate (0.78ml, 5.5mmol) and stirred at ambient temperature for 1 hour. The reaction mixture was diluted with ethyl acetate, washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography eluting with 0:1 – 1:4 methanol / ethyl acetate to afford the title compound. MS (ES+) m/e 351 $[M+H]^+$.

Step 4: (5*R*)-3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-5-(hydroxymethyl)-1,3-oxazolidin-2-one



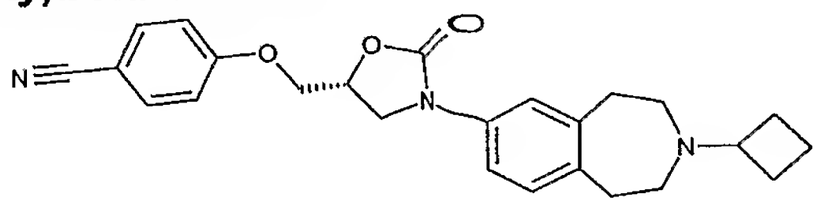
The title compound was prepared from phenylmethyl (3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)carbamate (product of E193, step 3) using the method described in WO 02/059115; MS (ES+) m/e 317 $[M+H]^+$.

Step 5: [(5*R*)-3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-2-oxo-1,3-oxazolidin-5-yl]methyl methanesulfonate



A solution of (5*R*)-3-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-5-(hydroxymethyl)-1,3-oxazolidin-2-one (product of E193, step 4) (0.40g, 1.3mmol) in dry dichloromethane (5ml) was treated with triethylamine (0.19ml, 1.4mmol) followed by methanesulphonyl chloride (0.11ml, 1.4mmol) and stirred at ambient temperature for 1.5 hours. The reaction mixture was diluted with dichloromethane, washed with saturated sodium hydrogen carbonate solution, dried ($MgSO_4$) and concentrated *in vacuo* to afford the title compound. MS (ES+) m/e 395 $[M+H]^+$.

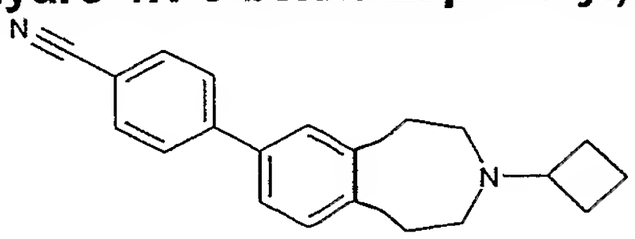
Step 6: 4-({[(5*R*)-3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-2-oxo-1,3-oxazolidin-5-yl]methyl}oxy)benzonitrile



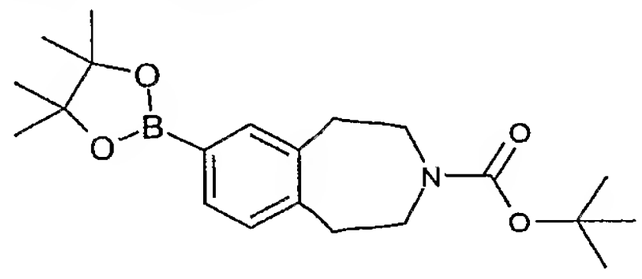
A solution of 4-cyanophenol (0.058g, 0.49mmole) in dry dimethylformamide (5ml) was treated with 60% sodium hydride in mineral oil (0.02g, 0.51mmole) and stirred for 0.5 hours at ambient temperature. [(5*R*)-3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-2-oxo-1,3-oxazolidin-5-yl]methyl methanesulfonate (product of E193, step 5) (0.2g, 0.51mmol) was added and the mixture stirred for 18 hours at 100°C. After cooling to ambient temperature, the reaction mixture was applied to a SCX ion exchange cartridge (Varian bond-elute) and washed with methanol and then 2M 0.880 ammonia/methanol. The basic fractions were concentrated *in vacuo*. The residue was purified by column chromatography eluting with dichloromethane / methanol (1:0 – 9:1) to afford the title compound. MS (ES+) m/e 418 $[M+H]^+$.

Example 194

4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)benzonitrile (E194)



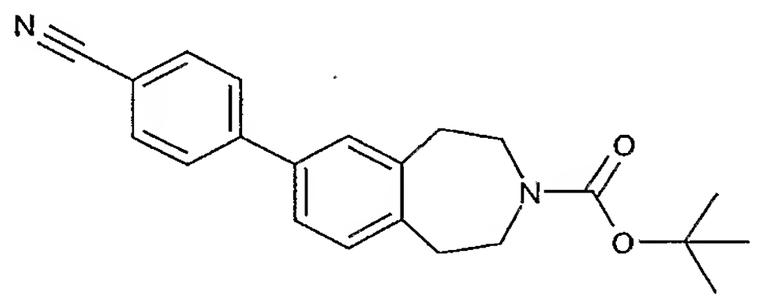
Step 1: 1,1-Dimethylethyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate



A mixture of 1,1-dimethylethyl-7-{[(trifluoromethyl)sulfonyl]oxy}-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (D1; Bioorganic and Medicinal Chemistry Letters (2000), 10(22), 2553-2555) (250mg, 0.63mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi-1,3,2-dioxaborolane (176mg,0.70mmol), 1,1'bis(diphenylphosphino)ferrocene dichloropalladium (II) complex (14mg, 0.02mmol), 1,1'bis(diphenylphosphino)ferrocene (11mg, 0.02mmol)

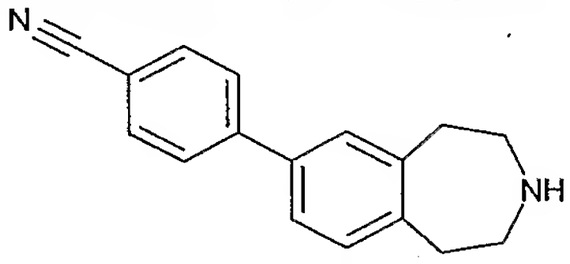
and potassium acetate (186mg, 2.00mmol) in dioxan (5ml) were heated in a microwave reactor at 140°C for 600 seconds at 200W. The mixture was diluted with ethyl acetate, washed with water (x3), then brine and dried over magnesium sulphate. The residue was purified by column chromatography eluting ethyl acetate/hexane (1:4) to afford the title compound. MS (ES+) m/e 274. $[M+H-100]^+$ (loss of carboxylate group).

Step 2: 1,1-Dimethylethyl 7-(4-cyanophenyl)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate



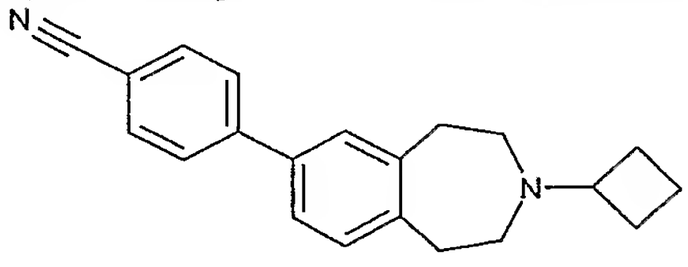
1,1-Dimethylethyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (product of E194, step 1) (180mg, 0.48mmol), 4-bromobenzonitrile (97mg, 0.53mmol), tetrakistriphenylphosphine palladium 17mg, 0.015mmol), sodium carbonate (102mg, 0.97mmol) and 1,2-dimethoxyethane/water/ethanol 7:3:1 (5ml) were heated in a microwave reactor at 160°C for 900 seconds at 200W. The mixture was diluted with ethyl acetate, washed with water (x3), then brine and dried over magnesium sulphate. The residue was purified by column chromatography eluting ethyl acetate/hexane (1:4) to afford the title compound. MS (ES+) m/e 249. $[M+H-100]^+$ (loss of carboxylate group).

Step 3: 4-(2,3,4,5-Tetrahydro-1*H*-3-benzazepin-7-yl)benzonitrile



1,1-Dimethylethyl 7-(4-cyanophenyl)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (product of E194, step 2) (203mg, 0.58mmol) was dissolved in dioxan (3ml) and hydrochloric acid in dioxan (4M; 5ml) was added. The reaction was stirred at room temperature for 24 hours. Solvent was then removed *in vacuo* and the product was dissolved in methanol and applied to a SCX cartridge (Varian bond-elute, 5 g) and washed with methanol and then a mixture of 2M ammonia/methanol. The basic fractions were combined and solvent was removed *in vacuo* to afford the title compound. MS (ES+) m/e 249 $[M+H]^+$.

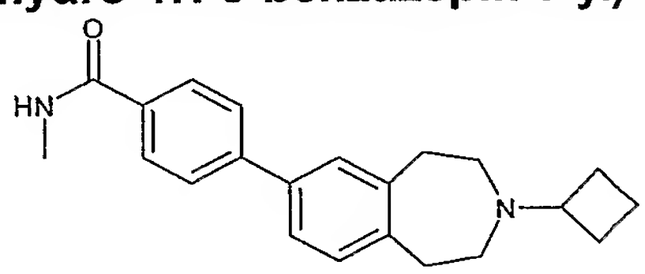
Step 4: 4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)benzonitrile



4-(2,3,4,5-Tetrahydro-1H-3-benzazepin-7-yl)benzonitrile (product of E194, step 3)(85mg, 0.34mmol), cyclobutanone (0.05ml, 0.68mmol), sodium triacetoxyborohydride (145mg, 0.68mmol) 4Å molecular sieves (50mg) and dichloromethane (5ml) were stirred at room temperature for 2 hours. The reaction mixture was filtered and solvent was removed *in vacuo.* The product was dissolved in methanol and applied to a SCX cartridge (Varian bond-elute, 5 g) and washed with methanol and then a mixture of 2M ammonia/methanol. The basic fractions were combined and solvent was removed *in vacuo* to afford the title compound. MS (ES+) m/e 303 $[M+H]^+$.

Example 195

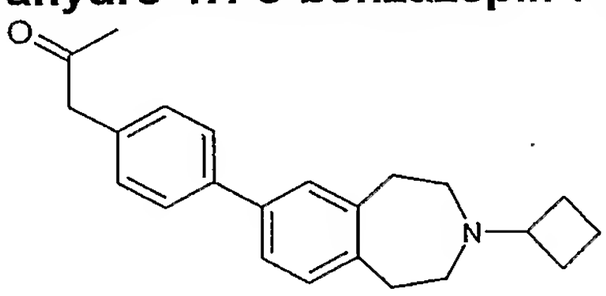
4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N–methylbenzamide (E195)



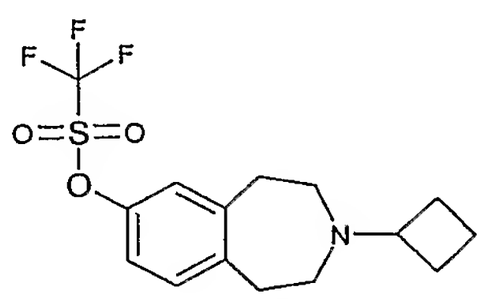
Example 195 was prepared using an analogous method to that described for Example 194 (steps 2-4) from 1,1-dimethylethyl 7-(4,4,5,5-tetramethyl-1,3,2–dioxaborolan-2-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (product of Example E194, step 1) and 4-bromo-N-methylbenzamide (WO 03/068749A1). MS (ES+) m/e 335 $[M+H]^+$.

Example 196

1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)phenyl]-2-propanone

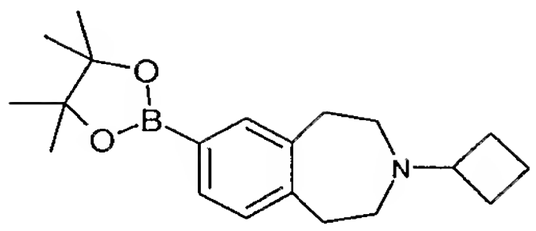


Step 1: 3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7–yl trifluoromethanesulfonate



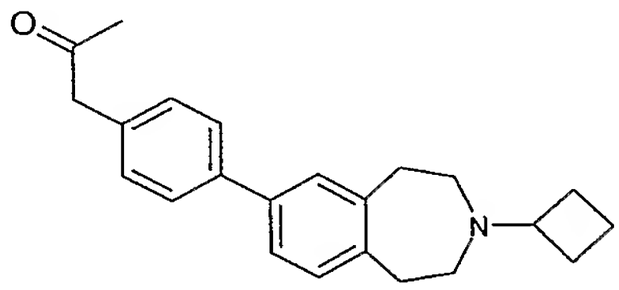
Step 1 was carried out using an analogous method to that described for Example 194 steps 3-4 using 1,1-dimethylethyl-7-{[(trifluoromethyl)sulfonyl]oxy}-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (D1) to afford the title compound. MS (ES+) m/e 350. $[M+H]^+$.

Step 2: 3-cyclobutyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3,4,5-tetrahydro-1H-3-benzazepine



Step 2 was carried out using an analogous method to that described for Example 194 step 1 using 3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl trifluoromethanesulfonate (product of E196, step 1) to afford the title compound. MS (ES+) m/e 328. $[M+H]^+$.

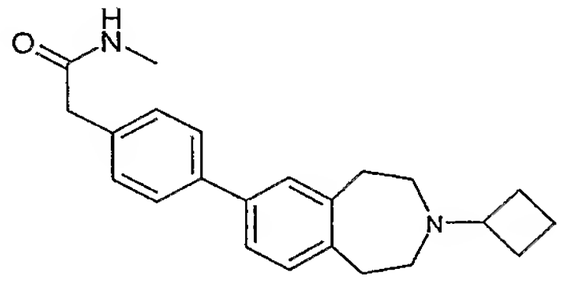
Step 3: 1-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)phenyl]-2-propanone



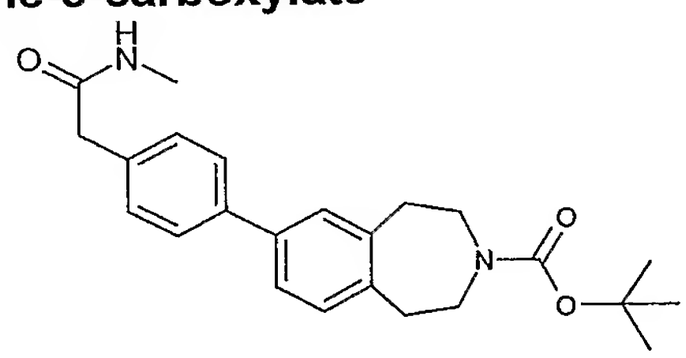
Step 3 was carried out using an analogous method to that described for Example 194 step 2 using 3-cyclobutyl-7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2,3,4,5-tetrahydro-1H-3-benzazepine (product of E196, step 2) (135mg, 0.41mmol) and 1-(4-bromophenyl)-2-propanone (97mg, 0.45mmol) to afford the title compound. MS (ES+) m/e 334. $[M+H]^+$.

Example 197

2-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)phenyl]-*N*-methylacetamide (E197)



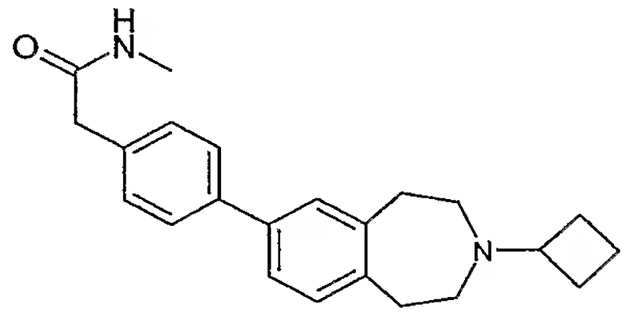
Step 1: 1,1-Dimethylethyl 7-{4-[2-(methylamino)-2-oxoethyl]phenyl}-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate



1,1-dimethylethyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (product of Example E194, Step 1) (379mg, 1.02mmol), 2-(4-bromophenyl)-*N*-methylacetamide (Tetrahedron (1966), 22(9), 2995-9) (255mg, 1.18mmol), tetrakistriphenylphosphine palladium (35mg, 0.030mmol), sodium carbonate (3.3ml, 2M) and 1,2-dimethoxyethane (10ml)) were heated at 80°C for 16 hours. The mixture was diluted with ethyl acetate, washed with water (x3), then brine and dried over magnesium sulphate. The residue was purified by column chromatography eluting 0-10%

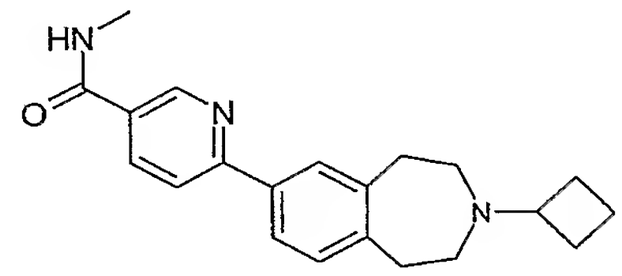
(2M ammonia in methanol / dichloromethane) to afford the title compound. MS (ES+) m/e 295. $[M+H-100]^+$ (loss of carboxylate group).

Step 2: 2-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)phenyl]-*N*-methylacetamide

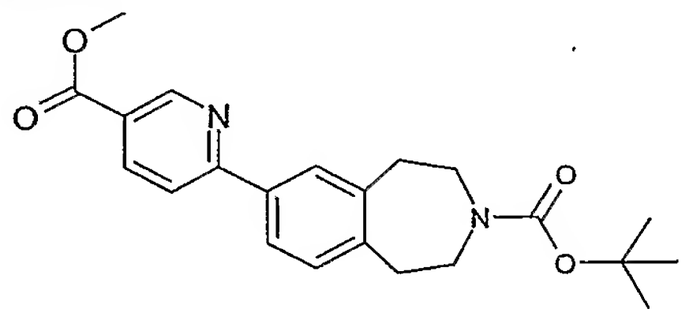


Step 2 was carried out using an analogous method to that described for Example 194 steps 3-4 using 1,1-dimethylethyl 7-{4-[2-(methylamino)-2-oxoethyl]phenyl}-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (product of E197, step 1). MS (ES+) m/e 349. $[M+H]^+$

Example 198
6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-methyl-3-pyridinecarboxamide (E198)

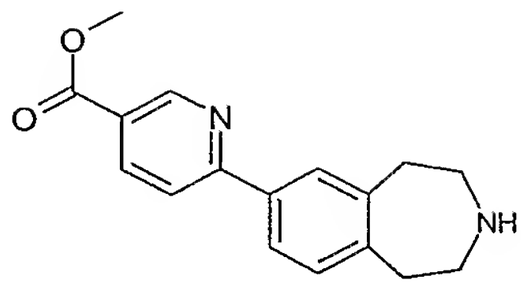


Step 1: 1,1-Dimethylethyl 7-{5-[(methyloxy)carbonyl]-2-pyridinyl}-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate



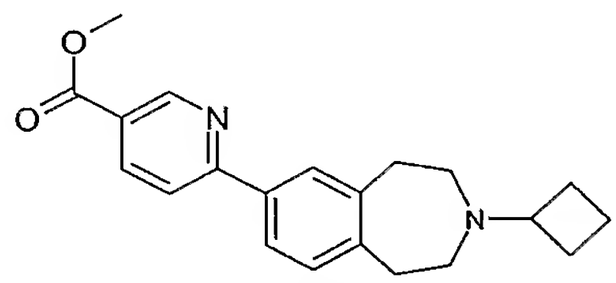
Step 1 was carried out using an analogous method to that described for Example 197 step 1 using 1,1-dimethylethyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (product of Example E194, Step 1) (888mg, 2.38mg), and methyl 6-chloro-3-pyridinecarboxylate (449mg, 2.62mmol).
^{1}H NMR (400MHz) $CDCl_3$ δ9.26 (1H (s) CH-Ar), δ8.34 (1H (d) CH-Ar), δ7.86 (1H (s) CH-Ar), δ7.80 (2H (d) CH-Ar), δ97.23 (1H (s) CH-Ar), δ3.97 (3H (s) CH_3), δ3.59 (4H (m) 2xCH_2), δ3.00 (4H (m) 2xCH_2), δ1.49 (9H (s) 3xCH_3).

Step 2: Methyl 6-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-3-pyridinecarboxylate



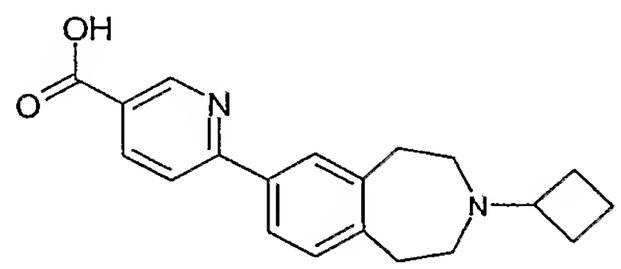
1,1-Dimethylethyl 7-{5-[(methyloxy)carbonyl]-2-pyridinyl}-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (product of E198, step 1) (495mg, 1.18mmol), was dissolved in dichloromethane (10ml), and the mixture was cooled to 0°C. Trifluoroacetic acid (3ml) was slowly added and the mixture was warmed to room temperature and stirred for 30 minutes. Solvent was removed *in vacuo* and the residue was dissolved in methanol, then applied to a SCX cartridge (Varian bond-elute, 10 g) and washed with methanol and then a mixture of 2M ammonia/methanol. The basic fractions were combined and solvent was removed *in vacuo* to afford the title compound. MS (ES+) m/e 283 $[M+H]^+$.

Step 3: Methyl 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-3-pyridinecarboxylate



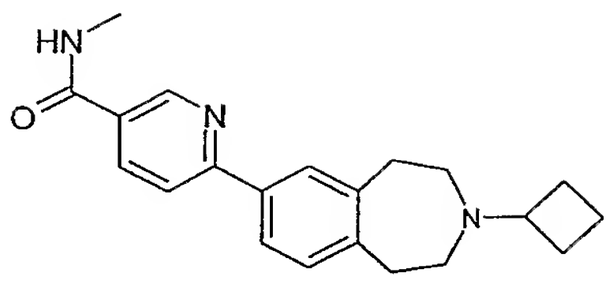
Step 3 was carried out using an analogous method to that described for Example 194 step 4 using methyl 6-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3-pyridinecarboxylate (product of E198, step 2). MS (ES+) m/e 337 $[M+H]^+$.

Step 4: 6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3-pyridinecarboxylic acid



Methyl 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3-pyridinecarboxylate (product of E198, step 3) (306mg, 0.91mmol), was dissolved in methanol (10ml) and lithium hydroxide (36mg, dissolved in 5ml water) was added. The mixture was stirred at room temperature for 24 hours. The solvent was removed *in vacuo* and the residue was azeotroped with ether to afford the title compound. MS (ES+) m/e 323 $[M+H]^+$

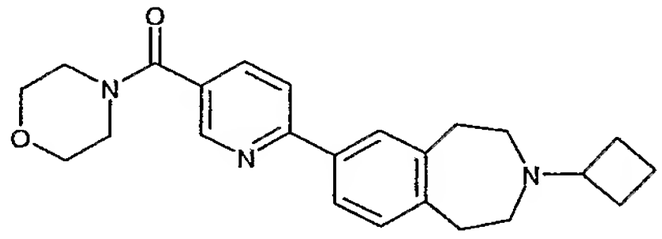
Step 5: 6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-*N*-methyl-3-pyridinecarboxamide



6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3-pyridinecarboxylic acid (product of E198, step 4) (180mg, 0.56mmol), methylamine (2M in tetrahydrofuran (2.7ml), HATU (206mg, 0.67mmol), triethylamine (0.2ml, 1.34mmol) and *N*,*N*-dimethylformamide (5ml) were stirred at room temperature for 16 hours. Solvent was removed *in vacuo* and the residue was dissolved in methanol. It was applied to a SCX cartridge (Varian bond-elute, 10 g) and washed with methanol and then a mixture of 2M ammonia/methanol. The basic fractions were collected and the product was purified further by column chromatography eluting 0-10% (2M ammonia in methanol / dichloromethane) to afford the title compound. MS (ES+) m/e 336. $[M+H]^+$.

Example 199

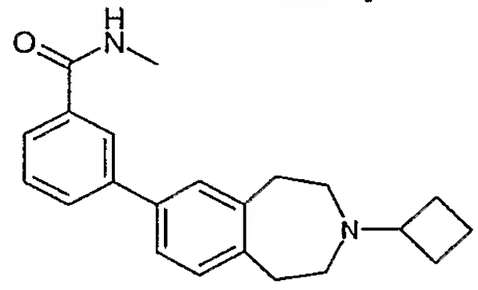
3-Cyclobutyl-7-[5-(4-morpholinylcarbonyl)-2-pyridinyl]-2,3,4,5-tetrahydro-1H-3-benzazepine (E199)



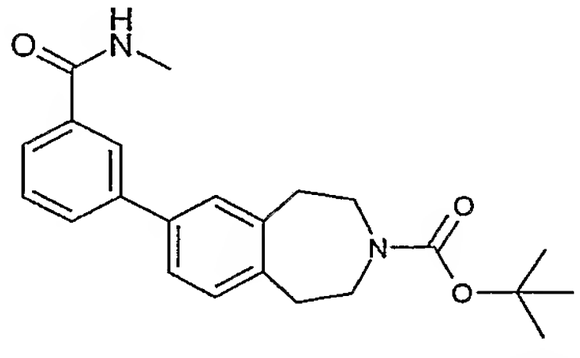
Example 199 was prepared using an analogous method to that described for Example 198 step 5 from 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3-pyridinecarboxylic acid (product of Example E198, Step 4) and morpholine. MS (ES+) m/e 392. $[M+H]^+$.

Example 200

3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-methylbenzamide (E200)



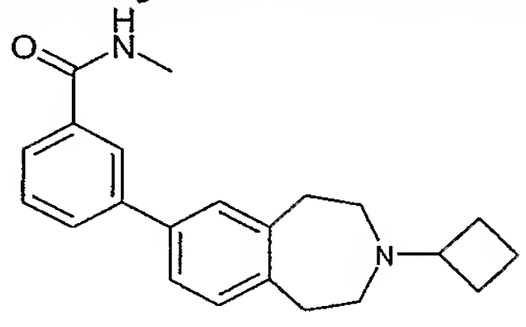
Step 1: 1,1-Dimethylethyl 7-{3-[(methylamino)carbonyl]phenyl}-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate



Step 1 was carried out using an analogous method to that described for Example 197 step 1 using 1,1-dimethylethyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4,5-tetrahydro-

3H-3-benzazepine-3-carboxylate (product of Example E194, Step 1) (300mg, 0.80mmol) and 3-bromo-N-methylbenzamide (189mg, 0.88mmol). ^{1}H NMR (400MHz) $CDCl_3$ δ7.98 (1H (s) CH-Ar), δ7.70 (2H (m) CH-Ar), δ7.49 (1H (t) CH-Ar), δ7.37 (2H (m) CH-Ar), δ7.21 (1H (s) CH-Ar), δ6.21 (1H (s) N-H), δ3.56 (4H (m) 2xCH_2), δ3.05 (3H (d) CH_3), δ2.95 (4H (m) 2xCH_2), δ1.49 (9H (s) 3xCH_3).

Step 2: 3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-methylbenzamide



Step 2 was carried out using an analogous method to that described for Example 98 steps 2-3 using 1,1-dimethylethyl 7-{3-[(methylamino)carbonyl]phenyl}-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (product of E200, step 1); MS (ES+) m/e 335. $[M+H]^+$.

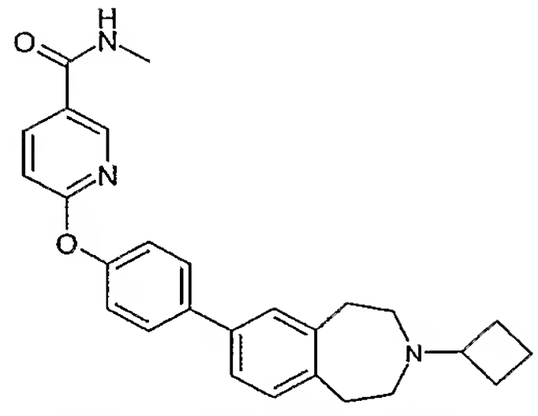
Example 201- 204 (E201-204)

Examples 201-204 were prepared using an analogous method to that described for Example 200 steps 1-2 from 1,1-dimethylethyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (product of Example E194, Step 1) and the appropriate halide indicated in the table below.

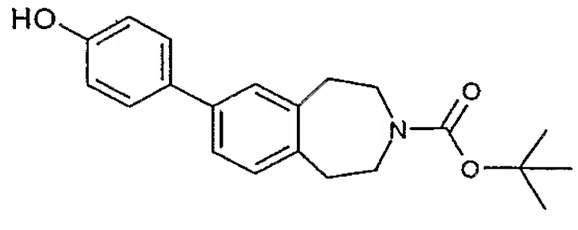
Example	Halide	LC/MS ($M+H^+$)
5-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-2-furancarbonitrile (E201)	5-bromo-2-furancarbonitrile	293
3-Cyclobutyl-7-(1,3-thiazol-2-yl)-2,3,4,5-tetrahydro-1H-3-benzazepine (E202)	2-bromo-1,3-thiazole	285
4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N,3-dimethylbenzamide (E203)	4-bromo-N,3-dimethyl benzamide (PCT Int. Appl. (1995), 19 pp. WO 9526328 A1)	353
4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3-fluoro-N-methylbenzamide (E204)	4-bromo-3-fluoro-N-methylbenzamide (D8)	349

Example 205

6-{[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)phenyl]oxy}-N-methyl-3-pyridinecarboxamide

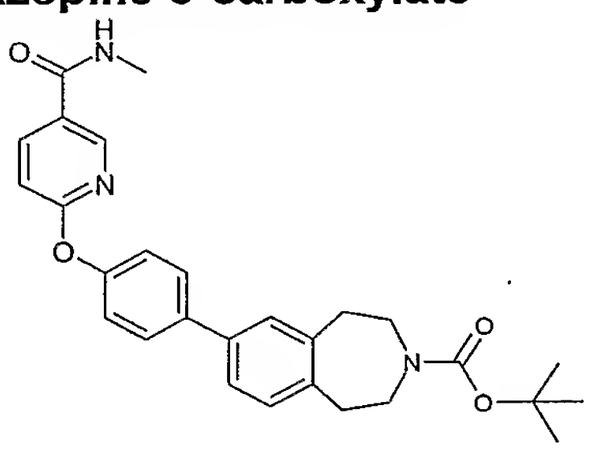


Step 1: 1,1-Dimethylethyl 7-(4-hydroxyphenyl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate



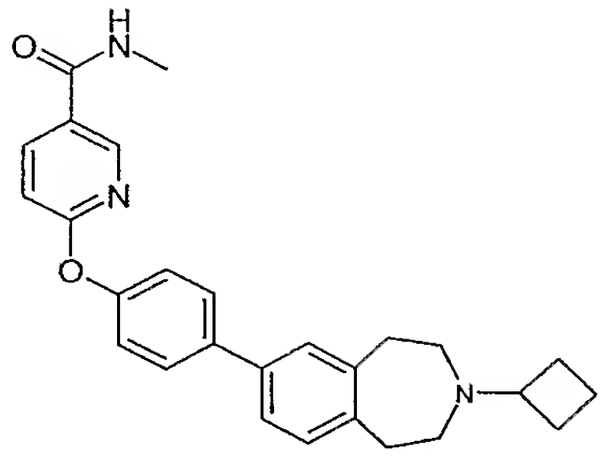
Step 1 was carried out using an analogous method to that described for Example 197 step 1 using 1,1-dimethylethyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (product of Example E194, Step 1) (1g, 2.68mmol) and 4-bromophenol (556mg, 3.21mmol). To afford the title compound. MS (ES+) m/e 340 $[M+H-100]^+$.

Step 2: 1,1-Dimethylethyl 7-[4-({5-[(methylamino)carbonyl]-2-pyridinyl}oxy)phenyl]-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate



1,1-Dimethylethyl 7-(4-hydroxyphenyl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (product of E205, step 1) (120mg, 0.35mmol) was dissolved in dimethylsulfoxide (10ml) and cooled to 0°C. Sodium hydride (25mg, 1.06mmol) was then added and the mixture was stirred for 30 minutes at 0°C. 6-chloro-*N*-methyl-3-pyridinecarboxamide (PCT Int. Appl. (2002), WO 2002046186)(181mg, 1.06mmol) was then added and the mixture was heated at 120°C for 48 hours. The reaction mixture was cooled to room temperature and poured onto ice/water, it was extracted into dichloromethane (x3), washed with water, then brine and dried using sodium sulphate. The product was purified by column chromatography eluting 5-20% (ethylacetate / hexane) to afford the title compound. MS (ES+) m/e 374 $[M+H-100]^+$ (loss of carboxylate group).

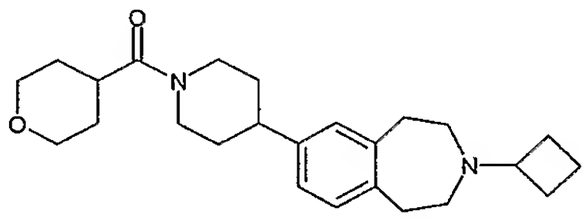
Step 3: 6-{[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)phenyl]oxy}-N-methyl-3-pyridinecarboxamide



Step 3 was carried out using an analogous method to that described for Example 198 steps 2-3 using 1,1-dimethylethyl 7-[4-({5-[(methylamino)carbonyl]-2-pyridinyl}oxy)phenyl]-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (product of E205, step 2) to afford the title compound. MS (ES+) m/e 428 $[M+H]^+$.

Example 206

3-cyclobutyl-7-[1-(tetrahydro-2*H*-pyran-4-ylcarbonyl)-4-piperidinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E206)



A mixture of tetrahydro-2*H*-pyran-4-carboxylic acid (62mg, 0.48mmol), *N*-Cyclohexylcarbodiimide *N'*-methyl polystyrene (282mg, 0.4mmol), and 1-hydroxybenzotriazole (65mg, 0.48mmol) in dry dimethylformamide (2ml) were stirred under argon at room temperature for 60 minutes. A solution of 3-cyclobutyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D12) (69mg, 0.24mmol) in dry dimethylformamide (0.5ml) was added, and the reaction mixture left to stir at room temperature for one day. The mixture was applied to a SCX ion exchange cartridge (Varian bond-elute, 5g), washed with methanol and then with a 2M ammonia in methanol solution. The combined basic fractions were concentrated *in vacuo* and the resulting residue purified by column chromatography eluting with a mixture of 2M ammonia in methanol and dichloromethane (1-2%) to afford the title product; MS (ES+) m/e 397 $[M+H]^+$.

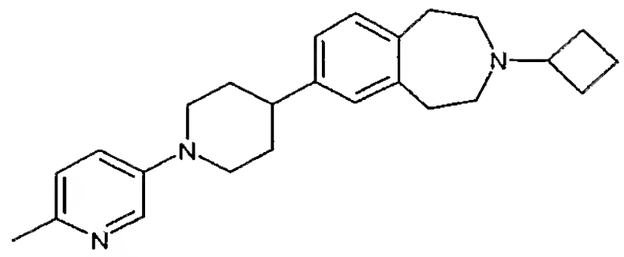
Examples 207-220 (E207-220)

Examples 207-220 (E207-E220) were prepared using an analogous method to that described for Example 206 (E206) from 3-cyclobutyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D12) and the appropriate carboxylic acid as indicated in the table.

Example	**Acid**	**LC/MS ($M+H^+$)**
5-{[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]carbonyl}-2-pyridinecarbonitrile (E207)	6-cyano-3-pyridinecarboxylic acid	415
3-{[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]carbonyl}benzonitrile	3-cyanobenzoic acid	413

(E208)		
3-cyclobutyl-7-[1-(2-pyrazinylcarbonyl)-4-piperidinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E209)	2-pyrazinecarboxylic acid	391
3-cyclobutyl-7-{1-[(4-fluorophenyl)carbonyl]-4-piperidinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E210)	4-fluorobenzoic acid	407
7-[1-(2,1,3-benzoxadiazol-5-ylcarbonyl)-4-piperidinyl]-3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E211)	2,1,3-benzoxadiazole-5-carboxylic acid	431
3-cyclobutyl-7-(1-{[6-(trifluoromethyl)-3-pyridinyl]carbonyl}-4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E212)	6-(trifluoromethyl)-3-pyridinecarboxylic acid	458
3-cyclobutyl-7-[1-(1,3-thiazol-4-ylcarbonyl)-4-piperidinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E213)	1,3-thiazole-4-carboxylic acid	396
3-cyclobutyl-7-{1-[(2-fluorophenyl)carbonyl]-4-piperidinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E214)	2-fluorobenzoic acid	407
3-cyclobutyl-7-[1-(2-pyridinylcarbonyl)-4-piperidinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E215)	2-pyridinecarboxylic acid	390
3-cyclobutyl-7-[1-(3-pyridinylcarbonyl)-4-piperidinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E216)	3-pyridinecarboxylic acid	390
3-cyclobutyl-7-[1-(pyrazolo[1,5-*a*]pyrimidin-3-ylcarbonyl)-4-piperidinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E217)	pyrazolo[1,5-*a*]pyrimidine-3-carboxylic acid	430
3-cyclobutyl-7-[1-(6-quinoxalinylcarbonyl)-4-piperidinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E218)	6-quinoxalinecarboxylic acid	441
3-cyclobutyl-7-[1-(5-quinoxalinylcarbonyl)-4-piperidinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E219)	5-quinoxalinecarboxylic acid	441
3-cyclobutyl-7-{1-[(6-methyl-3-pyridinyl)carbonyl]-4-piperidinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E220)	6-methyl-3-pyridinecarboxylic acid	404

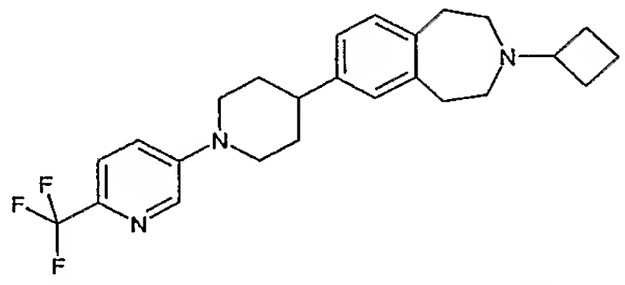
Example 221
3-cyclobutyl-7-[1-(6-methyl-3-pyridinyl)-4-piperidinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E221)



3-Cyclobutyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D12) (141mg, 0.50mmol), 5-bromo-2-methylpyridine (109mg, 0.63mmol), sodium *tert*-butoxide (34mg, 0.98mmol), tris(dibenzylideneacetone)dipalladium(0) (26mg, 0.04mmol) and 2'-(dicyclohexylphosphanyl)-*N*,*N*-dimethyl-2-biphenylamine (32mg, 0.11mmol) were mixed in 4ml of dry 1,4-dioxan. The reaction mixture was heated in microwave at 120°C for 10 min. The mixture was applied to a SCX ion exchange cartridge (Varian bond-elute, 5g), washed with methanol and then with a 2M ammonia in methanol solution. The combined basic fractions were concentrated *in vacuo* and the resulting residue purified by column chromatography eluting with a mixture of 2M ammonia in methanol and dichloromethane (4%) to give a yellow solid which was triturated with diethyl ether to afford the title product; MS (ES+) m/e 376 $[M+H]^+$.

Example 222

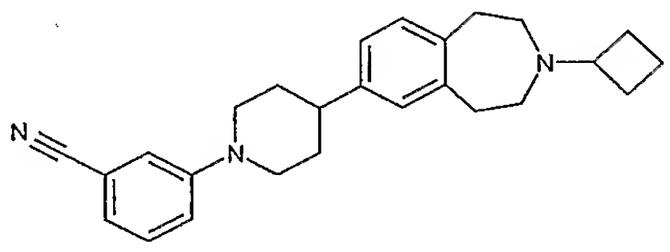
3-cyclobutyl-7-{1-[6-(trifluoromethyl)-3-pyridinyl]-4-piperidinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E222)



The title compound was prepared from 3-Cyclobutyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D12) and 5-bromo-2-(trifluoromethyl)pyridine using the same method described for the preparation of Example 221. MS (ES+) m/e 430 $[M+H]^+$.

Example 223

3-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]benzonitrile (E223)

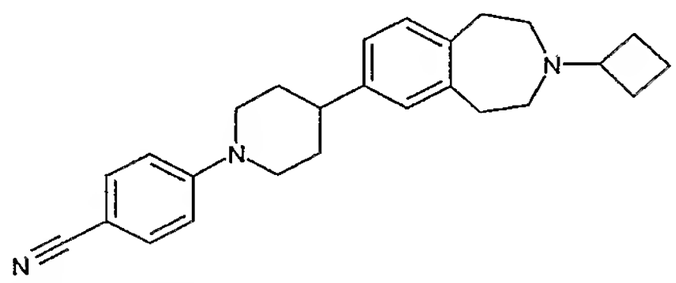


3-Cyclobutyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D12) (160mg, 0.56mmol), 3-bromobenzonitrile (108mg, 0.59mmol), cesium carbonate (255mg, 0.79mmol), palladium acetate (7mg, 0.03mmol) and (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphane) (26mg, 0.04mmol) were mixed in 2.5ml of toluene. The reaction mixture was heated in microwave at 140°C for 60 minutes. Ethyl acetate was added and the mixture filtered through celite, washed with brine, dried over anhydrous magnesium sulfate and concentrated *in vacuo*. The crude residue was purified by column

chromatography eluting with a mixture of 2M ammonia in methanol and dichloromethane (1-2%) to afford the title product; MS (ES+) m/e 386 $[M+H]^+$.

Example 224

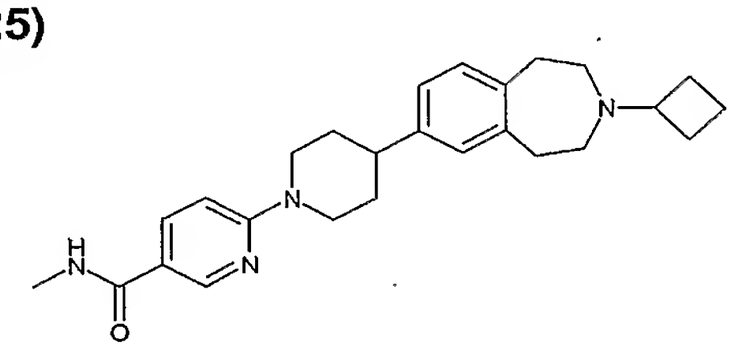
4-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]benzonitrile (E224)



3-Cyclobutyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D12) (143mg, 0.50mmol), 4-bromobenzonitrile (109mg, 0.60mmol), cesium carbonate (249mg, 0.76mmol), palladium acetate (12mg, 0.05mmol) and (9,9-dimethyl-9*H*-xanthene-4,5-diyl)bis(diphenylphosphane) (26mg, 0.04mmol) were mixed in 1.5ml of toluene and 1ml of acetonitrile. The reaction mixture was heated in microwave at 140°C for 120 minutes. The mixture filtered through celite and applied to a SCX ion exchange cartridge (Varian bond-elute, 5g), washed with methanol and then with a 2M ammonia in methanol solution. The combined basic fractions were concentrated *in vacuo* and the resulting residue purified by column chromatography eluting with a mixture of 2M ammonia in methanol and dichloromethane (3-5%) to afford the title product; MS (ES+) m/e 386 $[M+H]^+$.

Example 225

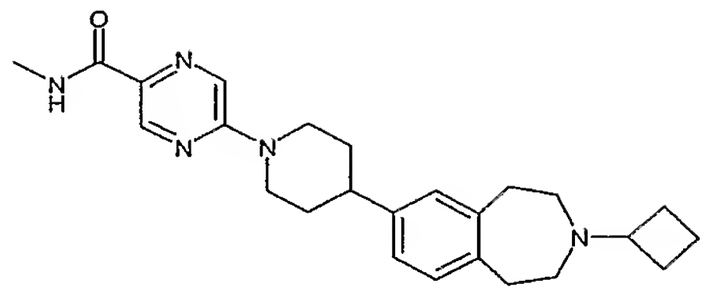
6-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-*N*-methyl-3-pyridinecarboxamide (E225)



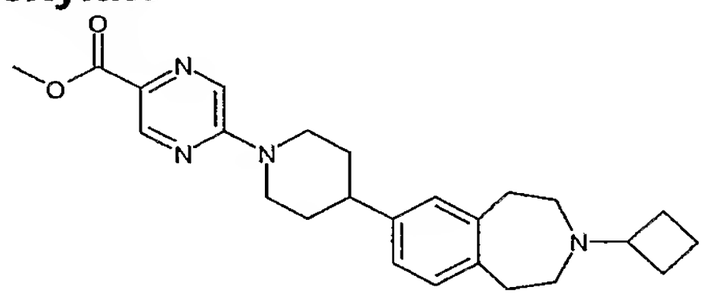
3-Cyclobutyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D12) (100mg, 0.35mmol), 6-chloro-N-methyl-3-pyridinecarboxamide (PCT Int. Appl. (2002), WO 2002046186) (72mg, 0.42mmol) and potassium carbonate (107mg, 0.77mmol) were mixed in 2ml of 1-methyl-2-pyrrolidinone. The reaction mixture was heated in microwave at 210°C for 30 minutes. The mixture was applied to a SCX ion exchange cartridge (Varian bond-elute, 5g), washed with methanol and then with a 2M ammonia in methanol solution. The combined basic fractions were concentrated *in vacuo* and the resulting residue purified by column chromatography eluting with a mixture of 2M ammonia in methanol and dichloromethane (1-3%) to afford the title product; MS (ES+) m/e 419 $[M+H]^+$.

Example 226

5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-*N*-methyl-2-pyrazinecarboxamide (E226)

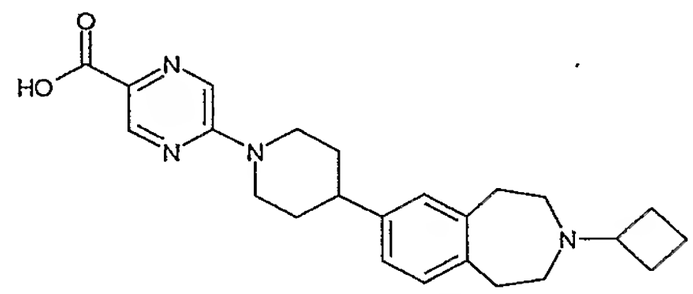


Step1: methyl 5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyrazinecarboxylate



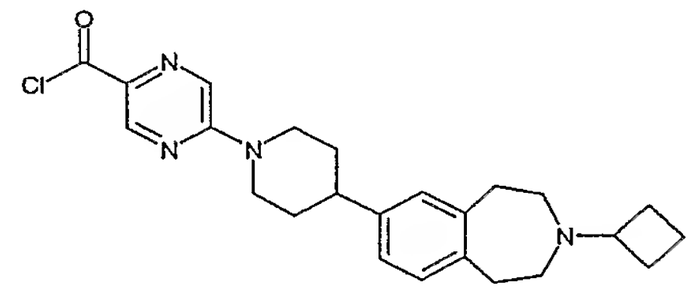
3-Cyclobutyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D12) (180mg, 0.63mmol), methyl 5-chloro-2-pyrazinecarboxylate (222mg, 1.27mmol) and potassium carbonate (183mg, 1.27mmol) were mixed in 5.5ml of 1-methyl-2-pyrrolidinone. The reaction mixture was heated in microwave at 210°C for 30 minutes. The mixture was applied to a SCX ion exchange cartridge (Varian bond-elute, 10g), washed with methanol and then with a 2M ammonia in methanol solution. The combined basic fractions were concentrated *in vacuo* and the resulting residue purified by column chromatography eluting with a mixture of 2M ammonia in methanol and dichloromethane (0-2%) to afford the title product; MS (ES+) m/e 421 $[M+H]^+$.

Step 2: 5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyrazinecarboxylic acid



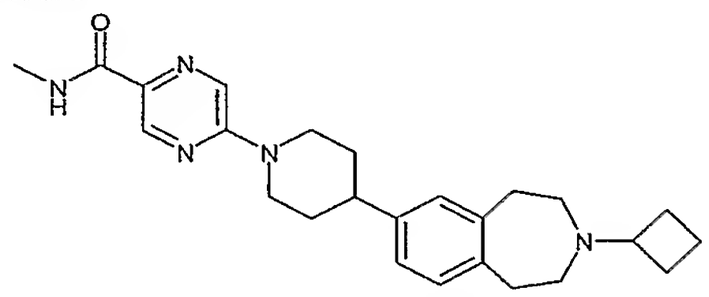
A solution of methyl 5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyrazinecarboxylate (product of E226, step 1) (167mg, 0.40mmol) in dichloromethane (2.5ml) was treated with conc. HCl (2.5ml) and the resulting biphasic mixture heated in a microwave at 100°C for 60 minutes. The mixture was concentrated *in vacuo* and azeotroped with toluene and dichloromethane to afford the crude product which was used directly in the next step.

Step 3: 5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyrazinecarbonyl chloride



A suspension of 5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyrazinecarboxylic acid (product of E226, step 2) (161mg, 0.40mmol) in dichloromethane (10ml) was treated with oxalyl chloride (0.15ml, 1.75mmol), followed by dimethylformamide (1 drop). The resulting clear solution was allowed to stir at room temperature for 1 hour. The mixture was then concentrated *in vacuo* and used directly in the next step.

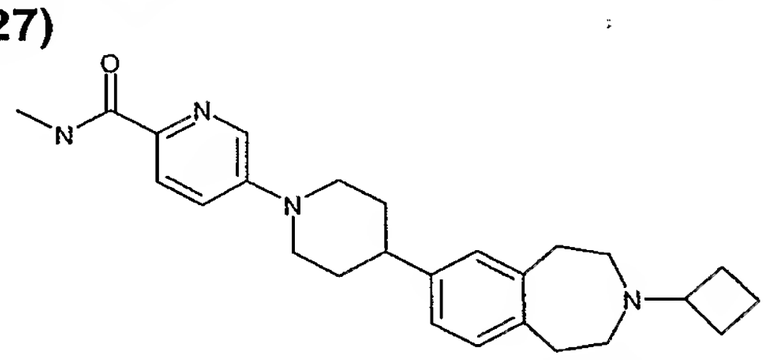
Step 4: 5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-*N*-methyl-2-pyrazinecarboxamide



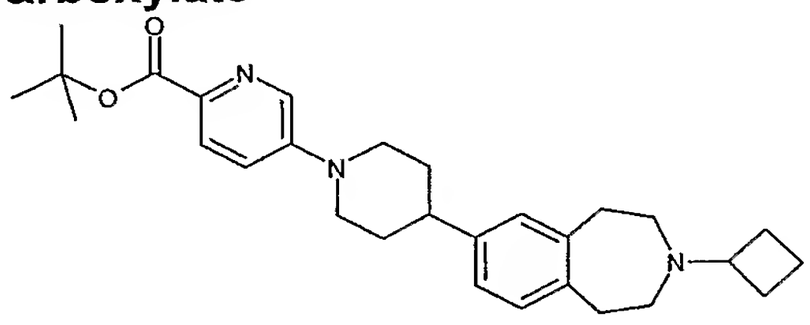
To a solution of 5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyrazinecarbonyl chloride (product of E226, step 3) (169mg, 0.397mmol) in dichloromethane (10ml) at 0°C was added, dropwise, a 2M solution of methylamine in THF (4ml, 7.94mmol). The mixture was allowed to stir at 0°C for 15 minutes and then at room temperature for 18 hours. The mixture was then concentrated *in vacuo* and purified by column chromatography eluting with a mixture of 2M ammonia in methanol and dichloromethane (2%). Recrystallisation from ethyl acetate afforded the title product; MS (ES+) m/e 420 $[M+H]^+$.

Example 227

5-[4-(3-cyclobutyl-2,3,4,5–tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-*N*-methyl-2-pyridinecarboxamide (E227)



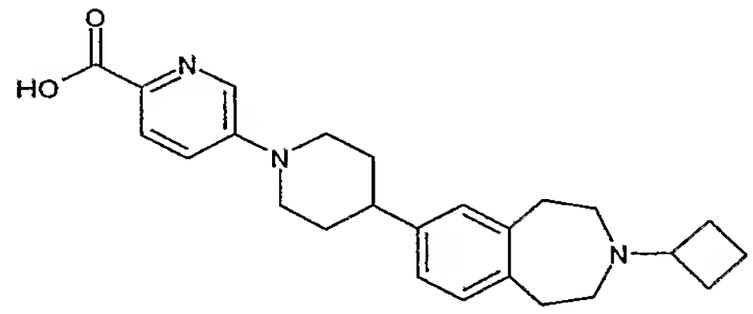
Step 1: 1,1-dimethylethyl 5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyridinecarboxylate



A mixture of 3-cyclobutyl-7–(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (285mg, 1.0mmol) (D12), 1,1-dimethylethyl 5-bromo-2-pyridinecarboxylate (351mg, 1.3mmol), tris (dibenzylidineacetone) dipalladium (23mg, 0.02mmol), caesium carbonate (482mg, 1.5mmol) and 'xantphos' (51mg, 0.1mmol) in 1,4-dioxan (8ml) was heated at reflux for 18 hours. The mixture was filtered through Celite and evaporated. The residue was purified by

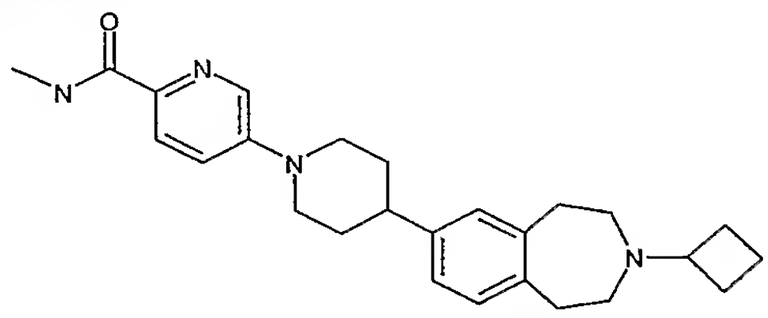
column chromatography on silica eluting with 97-3 dichloromethane – 2M ammonia in methanol to afford the title compound MS (AP+) m/e 462 $[M+H]^+$.

Step 2: 5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyridinecarboxylic acid



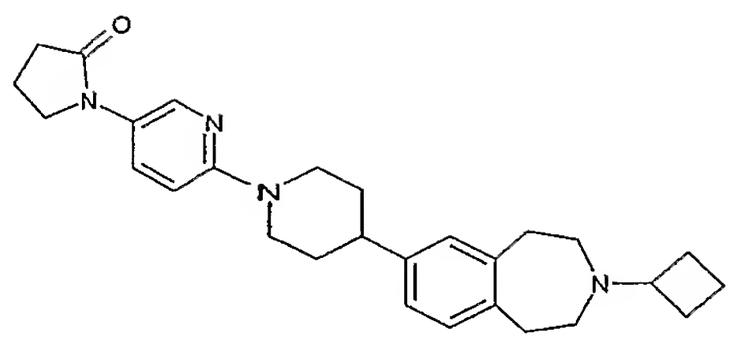
1,1-dimethylethyl 5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyridinecarboxylate (product of E227, step 1) (650mg, 1.4mmol) was dissolved in trifluoroacetic acid (20ml) and water (2ml) and stirred at room temperature for 5 hours. The solvent was removed by evaporation *in vacuo* to obtain the title compound as a yellow oil which was used crude in the next step.

Step 3: 5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-*N*-methyl-2-pyridinecarboxamide

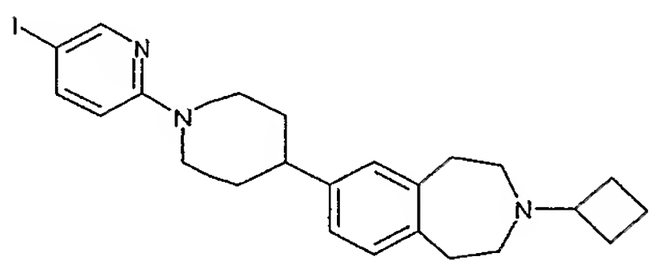


A mixture of 5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyridinecarboxylic acid (product of E227, step 2) (320mg, 0.79mmol) and 1,1'-(oxomethanediyl)bis-1*H*-imidazole (400mg, 2.5mmol) in dry tetrahydrofuran (5ml) was stirred at room temperature for 3 hours. A 2M solution of methylamine in tetrahydrofuran (10ml, 20mmol) was added and the mixture heated at 40°C for 18 hours. This was poured into water and extracted with ethyl acetate. The extracts were dried (sodium sulphate) and evaporated. The residue was purified on an SCX ion exchange cartridge eluting with methanol and then 2M ammonia in methanol to afford the title compound as a cream powder MS (AP+) m/e 419 $[M+H]^+$.

Example 228
1-{6-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-3-pyridinyl}-2-pyrrolidinone (E228)

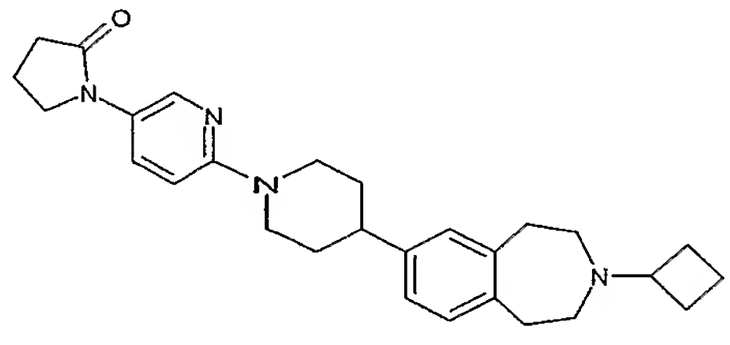


Step 1: 3-Cyclobutyl-7-[1-(5-iodo-2-pyridinyl)-4-piperidinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine



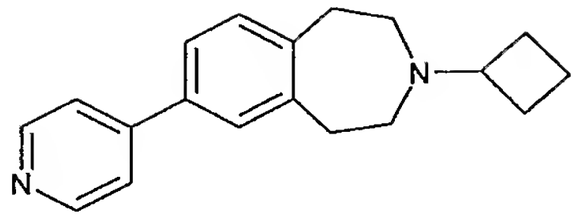
A mixture of 3-cyclobutyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D12) (79mg, 0.28mmol), 2-chloro-5-iodopyridine (107mg, 0.44mmol) and potassium carbonate (119mg, 0.87mmol) in *N*-methyl pyrrolidinone (4ml) was heated in a microwave reactor at 100°C (high absorbance) for 30 minutes and then at 180°C for 60 minutes. The mixture was purified on an SCX ion exchange cartridge eluting with methanol and then 2M ammonia in methanol. The basic fractions were combined and evaporated. The residue was purified by column chromatography on silica eluting with 98-2 dichloromethane – 2M ammonia in methanol to afford the title compound MS (AP+) m/e 488 $[M+H]^+$.

Step 2: 1-{6-[4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-3-pyridinyl}-2-pyrrolidinone

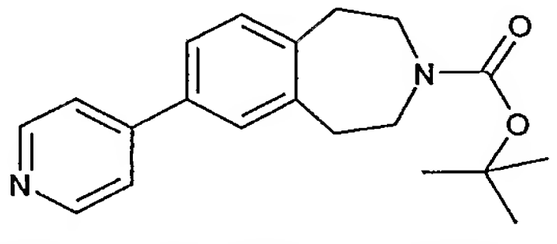


A mixture of 3-cyclobutyl-7-[1-(5-iodo-2-pyridinyl)-4-piperidinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (product of E228, step 1) (75mg, 0.15mmol), 2-pyrrolidinone (0.04ml, 0.52mmol), potassium carbonate (79mg, 0.55mmol), copper (I) iodide (18 mg, 0.09mmol) and *N*,*N*'-dimethyl-1,2-ethanediamine (0.02 ml, 0.18mmol) in 1,4-dioxan (3ml) was heated in a microwave reactor at 140°C (high absorbance) for 20 minutes. The mixture was purified on an SCX ion exchange cartridge eluting with methanol and then 2M ammonia in methanol. The basic fractions were combined and evaporated. The residue was purified by column chromatography on silica eluting with 97-3 dichloromethane – 2M ammonia in methanol to afford the title compound MS (AP+) m/e 445 $[M+H]^+$.

Example 229
3-Cyclobutyl-7-(4-pyridinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E229)

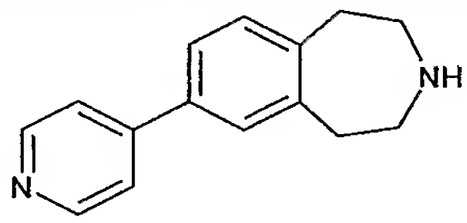


Step 1: 1,1-Dimethylethyl 7-(4-pyridinyl)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate



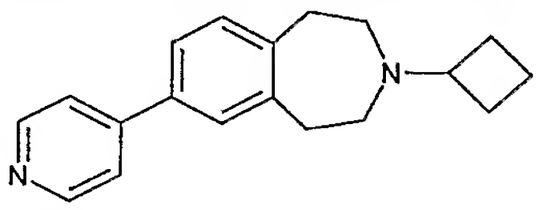
Tetrakis triphenylphosphino palladium (0) (375mg, 0.33mmol) was added to a mixture of 1,1-dimethylethyl 7-{[(trifluoromethyl)sulfonyl]oxy}-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D1) (1.29g, 3.25mmol) and 4-pyridinylboronic acid (0.6g, 5.0mmol) in dimethoxyethane (40ml) and 1M sodium carbonate solution (4ml). The resulting mixture was heated at reflux for 3 hours and allowed to cool to room temperature. The mixture was evaporated *in vacuo* and the residue purified by silica column chromatography eluting with 1-1 pentane – ethyl acetate to afford the title compound as a colourless crystalline solid (0.62g, 59%) MS (AP+) m/e 325 $[M+H]^+$.

Step 2: 7-(4-Pyridinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine



A solution of 1,1-dimethylethyl 7-(4-pyridinyl)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (product of E229, step 1) (1.15g, 3.54 mmol) in dichloromethane (10ml) was added drop-wise to a 4M solution of hydrogen chloride in dioxan (10ml). The resulting mixture was stirred at room temperature for 1 hour and was diluted with ethyl acetate. The resulting solid was collected by filtration and dissolved in water. The pH was adjusted to 12 by the addition of 2M sodium hydroxide solution and the mixture extracted with ethyl acetate. The extracts were combined, dried (sodium sulphate) and evaporated to give a colourless powder (0.52g, 66%) MS (AP+) m/e 225 $[M+H]^+$.

Step 3: 3-Cyclobutyl-7-(4-pyridinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine

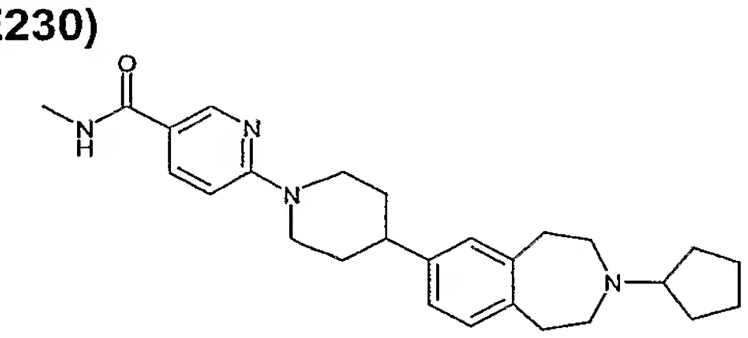


Sodium triacetoxyborohydride (0.38g, 1.8 mmol) was added to a mixture of 7-(4-pyridinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (product of E229, step 2) (0.2g, 0.9mmol) and cyclobutanone (0.33ml, 1.8mmol) in dichloromethane (3ml) and the mixture stirred for 3 days. The mixture was diluted with methanol and purified on an SCX ion exchange cartridge eluting with methanol and then 2M ammonia in methanol. The basic fractions were combined and evaporated, the residue was purified by column chromatography on

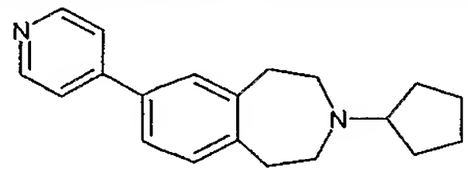
silica eluting with 97-3 dichloromethane – 2M ammonia in methanol to afford the title compound as a colourless crystalline solid (0.2 g, 80%) MS (AP+) m/e 279 $[M+H]^+$.

Example 230

6-[4-(3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-*N*-methyl-3-pyridinecarboxamide (E230)

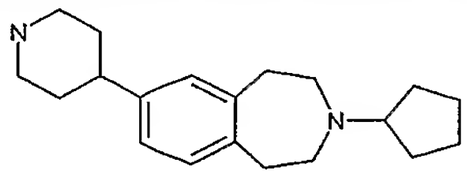


Step 1: 3-cyclopentyl-7-(4-pyridinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine



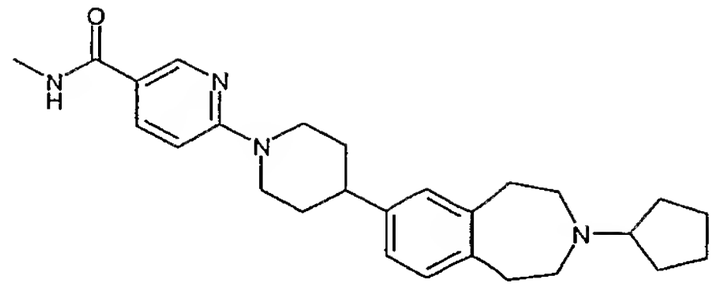
A mixture of 7-(4-pyridinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (3.74g, 16.7mmol) (product of E229, step 2), cyclopentanone (2.95ml, 33.3mmol), molecular sieves (4Å , 800 mg) and a 5% acetic acid/dichloromethane solution (120ml) was stirred at room temperature for 30 minutes. Sodium triacetoxyborohydride (7.0g, 33.3mmol) was then added and the mixture stirred at room temperature for 18 hours. The mixture was diluted with methanol and applied to a SCX ion exchange cartridge (Varian bond-elute, 10g), washed with methanol and then with a 2M ammonia in methanol solution. The combined basic fractions were concentrated *in vacuo* to afford the title product; MS (ES+) m/e 293 $[M+H]^+$.

Step 2: 3-cyclopentyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine



3-cyclopentyl-7-(4-pyridinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (product of E230, step 1) (4.8g, 16.4mmol) was dissolved in a mixture of ethanol:acetic acid (10:1) (198ml). Platinum oxide (480mg) was added and the reaction mixture was heated at 50°C under hydrogen (50 psi) for 24 hours. The mixture was then concentrated *in vacuo* and applied to a SCX ion exchange cartridge (Varian bond-elute, 10g), washed with methanol and then with a 2M ammonia in methanol solution. The combined basic fractions were concentrated *in vacuo* and purified by column chromatography eluting with a mixture of 2M ammonia in methanol and dichloromethane (5-10%) to afford the title product; MS (ES+) m/e 299 $[M+H]^+$.

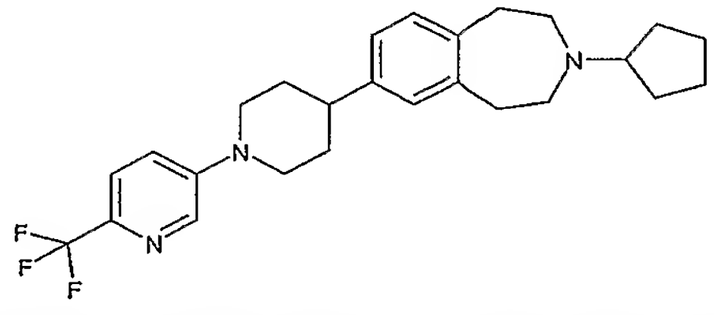
Step 3: 6-[4-(3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-*N*-methyl-3-pyridinecarboxamide



3-cyclopentyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (product of E230, step 2) (112mg, 0.38mmol), 6-chloro-N-methyl-3-pyridinecarboxamide (PCT Int. Appl. (2002), WO 2002046186)(84mg, 0.49mmol), and potassium carbonate (116mg, 0.83mmol) were mixed in 2ml of 1-methyl-2-pyrrolidinone. The reaction mixture was heated in microwave at 210°C for 30 minutes. The mixture was applied to a SCX ion exchange cartridge (Varian bond-elute, 10g), washed with methanol and then with a 2M ammonia in methanol solution. The combined basic fractions were concentrated *in vacuo* and the resulting residue purified by column chromatography eluting with a mixture of 2M ammonia in methanol and dichloromethane (1-3%) to afford the title product; MS (ES+) m/e 433 $[M+H]^+$.

Example 231

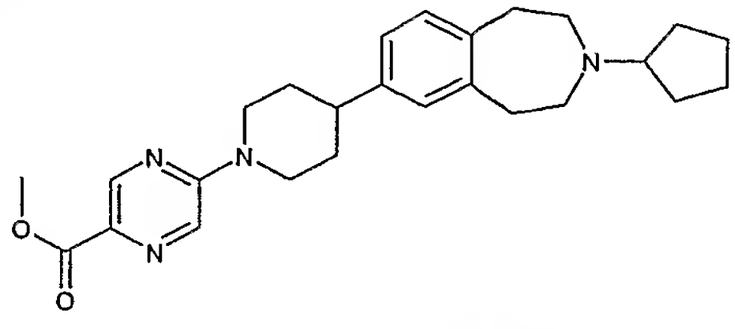
3-Cyclopentyl-7-{1-[6-(trifluoromethyl)-3-pyridinyl]-4-piperidinyl}-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E231)



3-Cyclopentyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (product of E230, step 2) (0.1g, 0.33mmol), 2-trifluoromethyl-5-bromo pyridine (83mg, 0.37mmol), tris (dibenzylidineacetone) dipalladium (13mg, 0.02 mmol 2'-(dicyclohexylphosphanyl)-*N*,*N*-dimethyl-2-biphenylamine (20mg, 0.06mmol) and sodium *tert*-butoxide (63mg, 0.66mmol) in dioxan (3ml) was heated in a microwave reactor at 120°C for 5 minutes. The crude mixture was purified on an SCX ion exchange cartridge eluting with methanol and then 2M ammonia in methanol. The basic fractions evaporated and the residue purified by column chromatography on silica eluting with 95-5 dichloromethane – 2M ammonia in methanol to afford the title compound as a yellow solid (46 mg, 31%) MS (AP+) m/e 444 $[M+H]^+$.

Example 232

Methyl 5-[4-(3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyrazinecarboxylate (E232)

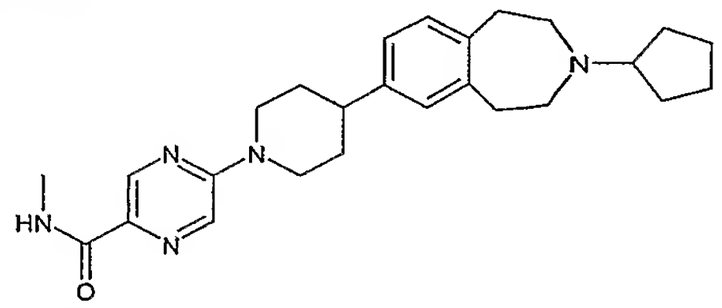


A mixture of 3-Cyclopentyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (product of E230, step 2) (0.5g, 1.68mmol), potassium carbonate (0.46g, 3.35mmol) and methyl 5-

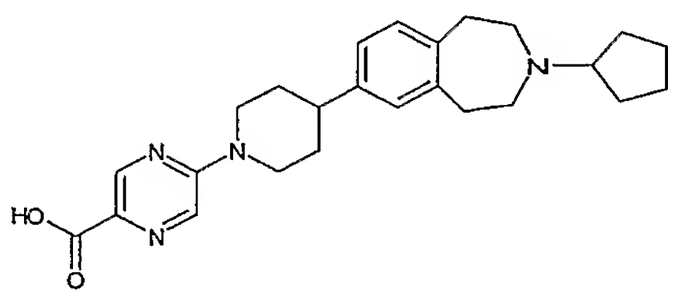
chloro-2-pyrazinecarboxylate (0.58g, 3.35mmol) in dimethylformamide (20ml) was heated at 90°C for 3 hours. The crude mixture was purified on an SCX ion exchange cartridge eluting with methanol and then 2M ammonia in methanol. The basic fractions evaporated and the residue purified by column chromatography on silica eluting with 95-5 dichloromethane – 2M ammonia in methanol to afford the title compound as a yellow solid (0.55 g, 75%) MS (AP+) m/e 435 $[M+H]^+$.

Example 233

5-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-*N*-methyl-2-pyrazinecarboxamide (E233)

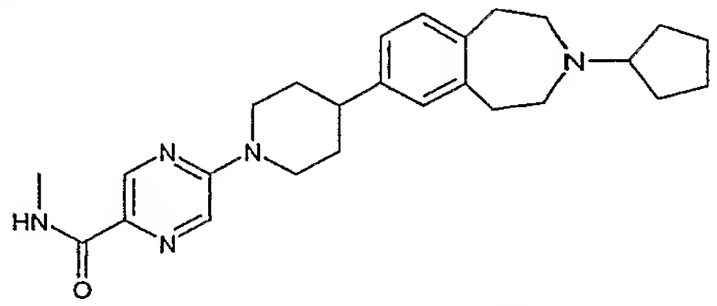


Step 1: 5-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyrazinecarboxylic acid



A solution of methyl 5-[4-(3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyrazinecarboxylate (E232) (100mg, 0.23mmol) in methanol (5ml) was treated with 1M sodium hydroxide solution (1ml) and heated at reflux for 90 minutes. The mixture was acidified using 2 M hydrochloric acid and purified on an SCX ion exchange column eluting with methanol and then 2M ammonia in methanol. The basic fractions were evaporated to afford the title compound as a yellow solid MS (AP+) m/e 421 $[M+H]^+$.

Step 2: 5-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-*N*-methyl-2-pyrazinecarboxamide

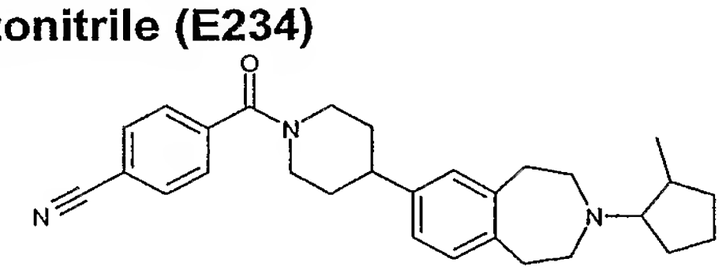


A solution of 5-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyrazinecarboxylic acid (product of E233, step 1) (100mg, 0.24mmol) in tetrahydrofuran (3ml) was treated with *N,N'*-dicyclohexylcarbodiimide (39mg, 0.24mmol) and stirred at room temperature for 18 hours. This mixture was treated with 2M methylamine in tetrahydrofuran (0.24ml, 0.48mmol) and stirred at room temperature for 18 hours. The mixture was purified on an SCX ion exchange column eluting with methanol and then 2M ammonia in methanol.

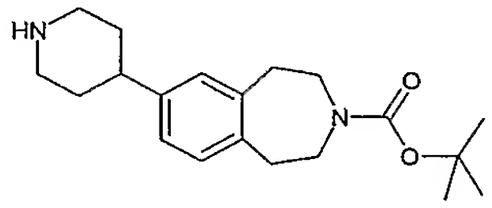
The basic fractions were evaporated to afford the title compound as a colourless solid MS (AP+) m/e 434 $[M+H]^+$.

Example E234

4-({4-[3-(2-methylcyclopentyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl]-1-piperidinyl}carbonyl)benzonitrile (E234)

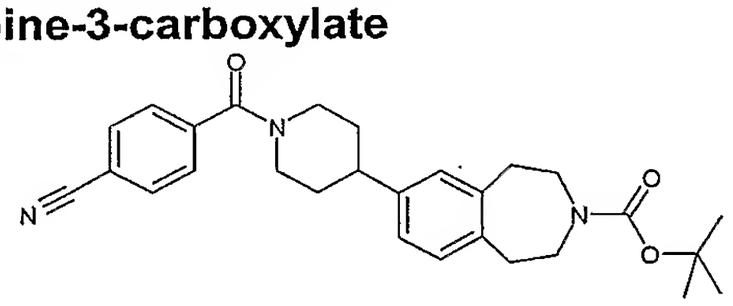


Step 1: 1,1-dimethylethyl 7-(4-piperidinyl)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate



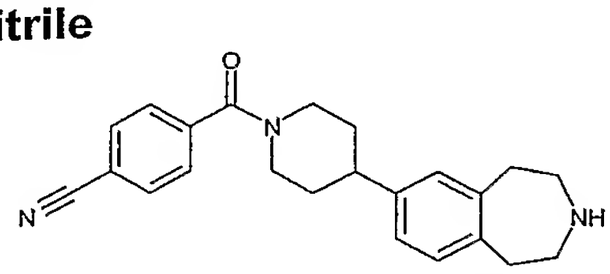
1,1-Dimethylethyl 7-(1-{[(phenylmethyl)oxy]carbonyl}-1,2,3,6-tetrahydro-4-pyridinyl)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (D9) (2.09g, 4.52mmol) was dissolved ethanol (140ml). Palladium on charcoal (720mg, 10% palladium/charcoal paste) was added and the reaction mixture was heated at 40°C under hydrogen (50 psi) for 24 hours. The mixture was then filtered through celite and concentrated *in vacuo*. The resulting oil was re-dissolved in dichloromethane and evaporated three times and then re-dissolved in diethyl ether and evaporated twice to yield the title product; MS (ES+) m/e 331 $[M+H]^+$.

Step 2: 1,1-dimethylethyl 7-{1-[(4-cyanophenyl)carbonyl]-4-piperidinyl}-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate



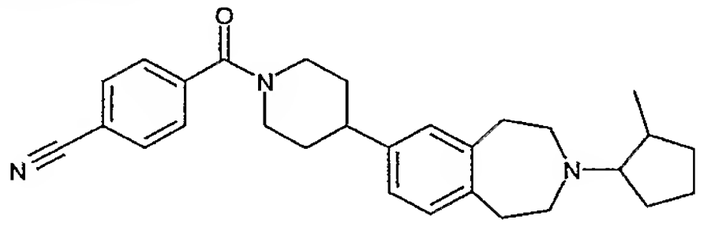
A mixture of 4-cyanobenzoic acid (1.39g, 4.66mmol), *N*-Cyclohexylcarbodiimide *N'*-methyl polystyrene (4.48g, 9.32mmol), and 1-hydroxybenzotriazole (1.25g, 9.32mmol) in dry dimethylformamide (20ml) were stirred under argon at room temperature for 60 minutes. A solution of 1,1-dimethylethyl 7-(4-piperidinyl)-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (product of E234, step 1)(1.54g, 4.66mmol) in dry dimethylformamide (10ml) was added, and the reaction mixture left to stir at room temperature for 3 hours. The mixture was filtered, diluted with water (60ml) and extracted with ethyl acetate (4 x 60ml). The combined organic phases were washed with a saturated sodium bicarbonate solution (2 x 60ml) and brine (2 x 60ml). The organic phase was dried over magnesium sulphate and concentrated *in vacuo*. The resulting residue was purified by column chromatography eluting with a mixture of ethyl acetate in pentane (20-50%) to afford the title product; MS (ES+) m/e 360 $[M-BOC]^+$.

Step 3: 4-{[4-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]carbonyl}benzonitrile



1,1-dimethylethyl 7-{1-[(4-cyanophenyl)carbonyl]-4-piperidinyl}-1,2,4,5-tetrahydro-3*H*-3-benzazepine-3-carboxylate (product of E234, step 2) (1.61g, 3.51mmol) was dissolved in dichloromethane (5ml) at 0°C and treated with trifluoroacetic acid (5ml). The solution was stirred at room temperature for 5 hours and concentrated *in vacuo*, co-evaporating with dichloromethane. The residue was re-dissolved in dichloromethane and ammonia 0.88 (10ml) was added. The organic phase was separated and the aqueous phase extracted with dichloromethane (4 x 10ml). The combined organic phases were washed with water (10ml), dried over magnesium sulphate and concentrated *in vacuo* to yield a yellow oil which was co-evaporated with diethyl ether to afford the title compound. MS (ES+) m/e 360 $[M+H]^+$.

Step 4: 4-({4-[3-(2-methylcyclopentyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl]-1-piperidinyl}carbonyl)benzonitrile



4-{[4-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]carbonyl}benzonitrile (product of E234, step 3)(160 mg, 0.45mmol) was dissolved in anhydrous dichloromethane (3ml) and treated with 2-methylcyclopentanone (0.1ml, 0.93mmol), followed by acetic acid (0.5ml). The reaction mixture was allowed to stir at room temperature for one hour. Sodium triacetoxyborohydride (250mg, 1.32mmol) was added and the reaction mixture stirred at room temperature for 18 hours. The mixture was diluted with methanol and applied to a SCX cartridge (Varian bond-elute, 5 g) and washed with methanol and then a mixture of 2M ammonia/methanol. The basic fractions were combined and solvent was removed *in vacuo*. The resulting residue was purified by column chromatography eluting with a mixture of methanol and dichloromethane (0-10%) to afford the title product; MS (ES+) m/e 442 $[M+H]^+$.

Example 235-236 (E235-E236)

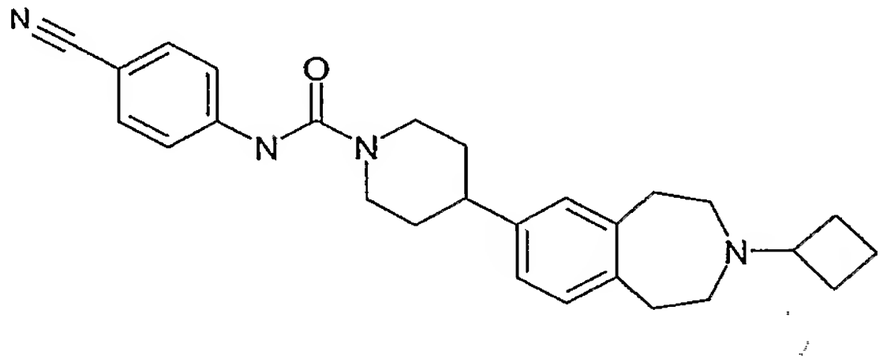
Examples 235-236 were prepared using an analogous method to that described for Example 234 step 4 from 4-{[4-(2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]carbonyl}benzonitrile (product of E234, step 3) and the appropriate ketone indicated in the table below.

Example	Ketone	LC/MS ($M+H^+$)
4-{[4-(3-cyclohexyl-2,3,4,5-tetrahydro-1H-3-	cyclohexanone	441

benzazepin-7-yl)-1-piperidinyl]carbonyl}benzonitrile(E235)		
4-{[4-(3-cyclopentyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-piperidinyl]carbonyl}benzonitrile (E236)	cyclopentanone	428

Example 237

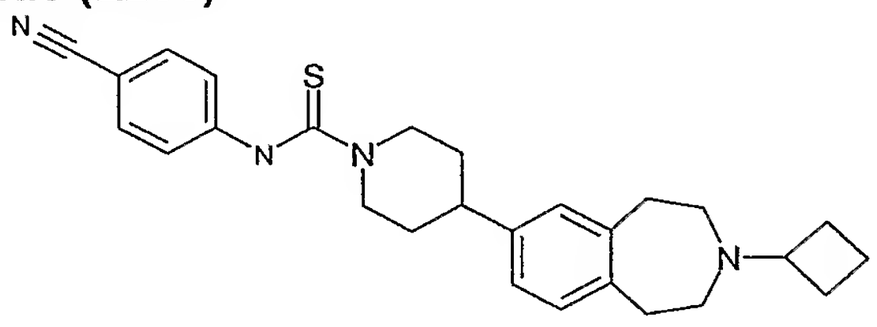
N-(4-cyanophenyl)-4-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7–yl)-1-piperidinecarboxamide (E237)



4-Aminobenzonitrile (0.059g, 0.50mmol) in dry dichloromethane (5ml) was added dropwise to a 20% solution of phosgene in toluene (0.36ml, 0.75mmol) and the mixture was stirred at room temperature for 30 minutes. The solvents were removed *in vacuo* and the residue dissolved in dichloromethane (5ml) and treated with diisopropylethlamine (0.12ml, 0.25mmol) followed by 3-cyclobutyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (D12) (0.07g, 0.25mmol) in dichloromethane (1ml). The mixture was stirred at room temperature for 2 hours after which it was diluted with methanol and applied to an SCX cartridge (Varian bond-elute) and washed with methanol and then a mixture of 2M ammonia/methanol. The basic fractions were combined and the solvent removed *in vacuo*. The residue was purified by column chromatography eluting with a gradient of dichloromethane to 6% (2M 0.880 ammonia/methanol)/dichloromethane to afford the title compound; MS (ES+), m/e 429 $[M+H]^+$

Example 238

N-(4-Cyanophenyl)-4-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7–yl)-1-piperidinecarbothioamide (E238)

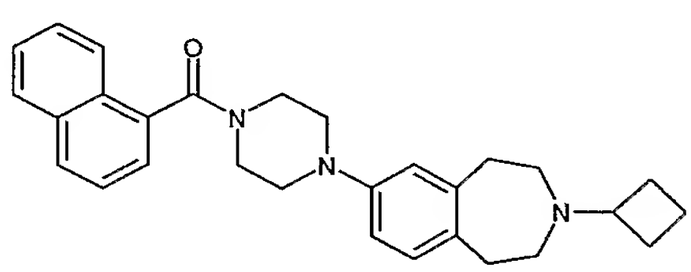


3-Cyclobutyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (D12) (0.15g, 0.52mmol) and 4-isothiocyanatobenzonitrile (0.13g, 0.8mmol) in dry dimethylformamide (10ml) were stirred at room temperature for 3 hours. The reaction mixture was diluted with methanol and applied to an SCX cartridge (Varian bond-elute) and washed with methanol

and then a mixture of 2M ammonia/methanol. The basic fractions were combined and the solvent removed *in vacuo* to afford the title compound; MS (ES+), m/e 445 $[M+H]^+$

Example 239

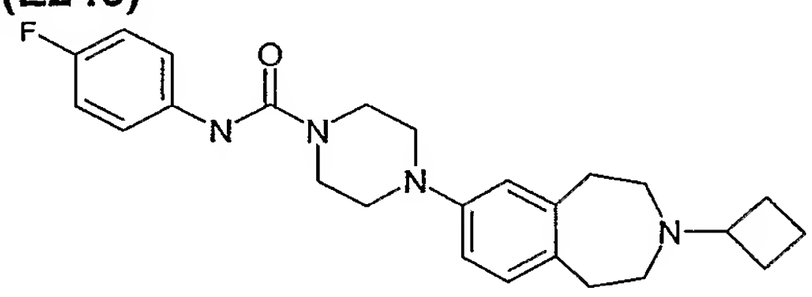
3-cyclobutyl-7-[4-(1-naphthalenylcarbonyl)-1-piperazinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E239)



3- Cyclobutyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (D7) (10mg, 0.04mmol) was dissolved in dichloromethane (1ml) and treated with 1-naphthalenecarboxylic acid (7mg, 0.04mmol) and di*iso*propylethylamine (7μl, 0.04mmol). The reaction mixture was then passed through an aminopropyl cartridge and purified using reverse phase chromatography to yield the title product, MS (ES+) m/e 440 $[M+H]^+$.

Example 240

4-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-(4-fluorophenyl)-1-piperazinecarboxamide (E240)



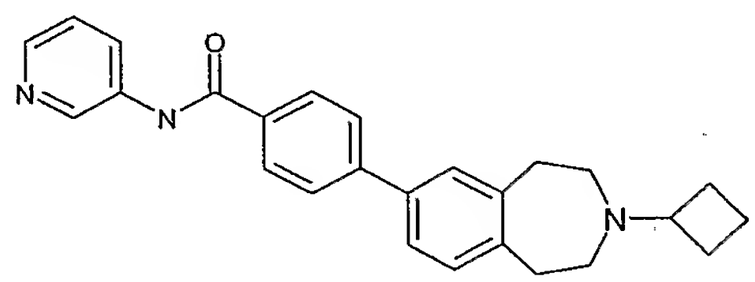
Diisopropylethylamine (0.15ml, 0.86mmol) in dry THF (3ml) was cooled to 0°C and treated with triphosgene (0.052g, 0.18mmol). The mixture was stirred for 5 minutes and treated dropwise with a solution of 3- cyclobutyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (D7) (0.10g, 0.36mmole) and diisopropylethylamine (0.15ml, 0.86mmol). After stirring for 20 minutes, 4-fluoroaniline (0.034ml, 0.35mmol) was added dropwise and the mixture was stirred overnight at room temperature. Ethyl acetate was added to the reaction mixture, which was subsequently filtered through celite. The filtrate was washed with water and brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was dissolved in methanol and applied to an SCX cartridge (Varian bond-elute) and washed with methanol and then a mixture of 2M ammonia/methanol. The basic fractions were combined and the solvent removed *in vacuo*. The residue was triturated with dichloromethane and the resulting solid filtered and dried to afford the title compound; MS (ES+), m/e 423 $[M+H]^+$

Examples 241 to 244

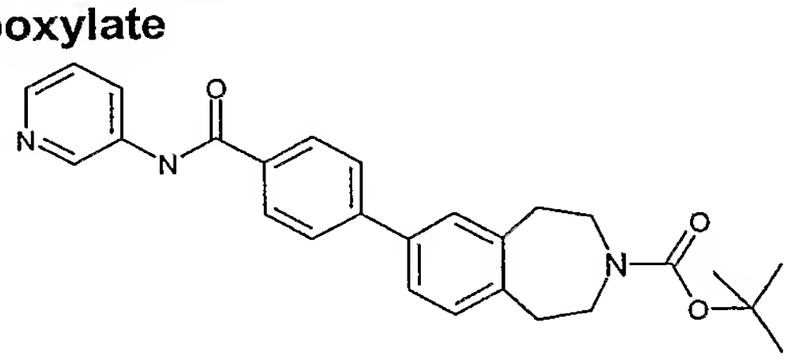
Examples 241 to 244 were prepared using an analogous method to that described for Example 240 from 3-cyclobutyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1H-3-benzazepine (D12) and the appropriate amine as indicated in the table.

Example	Amine	LC/MS $(M+H)^+$
4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-[4-(methyloxy)phenyl]-1-piperidinecarboxamide (E241)	4-Methoxyaniline	434
N-(3-Cyanophenyl)-4-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-piperidinecarboxamide (E242)	3-Aminobenzonitrile	429
3-Cyclobutyl-7-[1-(1,3-dihydro-2H-isoindol-2-ylcarbonyl)-4-piperidinyl]-2,3,4,5-tetrahydro-1H-3-benzazepine (E243)	Isoindoline	430
N-(6-cyano-3-pyridinyl)-4-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-1-piperidinecarboxamide (E244)	5-Amino-2-cyanopyridine	430

Example 245
4-(3-cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-3-pyridinylbenzamide (E245)

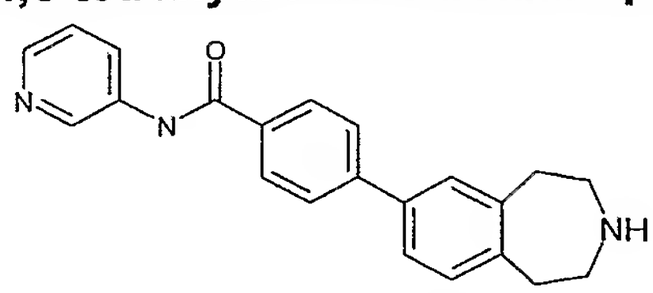


Step 1: 1,1-Dimethylethyl 7-{4-[(3-pyridinylamino)carbonyl]phenyl}-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate



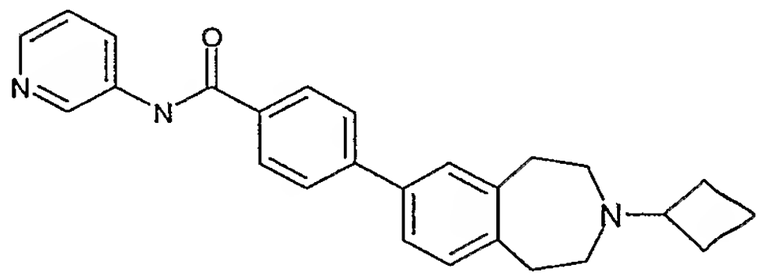
4-Iodo-*N*-3-pyridinylbenzamide (D13) (0.086g, 0.32mmole) in dimethoxyethane (7ml) and 2M aqueous sodium carbonate solution (0.23ml) was treated with 1,1-dimethylethyl 7-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (E194 Step 1) (0.10g, 0.27mmol) and tetrakis(triphenyl phosphinepalladium(0)) (0.009g, 0.008mmol) and heated at 80°C for 18 hours. The reaction mixture was partitioned between ethyl acetate and water and the ethyl acetate layer dried ($MgSO_4$) and concentrated *in vacuo*. The residue was purified by column chromatography eluting with a gradient of dichloromethane to 10% (2M 0.880 ammonia/methanol)/dichloromethane to afford the title compound; MS (ES+), m/e 344 $[M\text{-}BOC+H]^+$

Step 2: N-3-Pyridinyl-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)benzamide



1,1-Dimethylethyl 7-{4-[(3-pyridinylamino)carbonyl]phenyl}-1,2,4,5-tetrahydro-3H-3-benzazepine-3-carboxylate (product of E245, step 1) (0.059g, 0.13mmol) in dichloromethane (5ml) was cooled to 0°C and treated dropwise with trifluoroacetic acid (1ml). The mixture was stirred at room temperature for 1 hour after which the solvent was removed *in vacuo* and the residue dissolved in methanol and applied to an SCX cartridge (Varian bond-elute) and washed with methanol and then a mixture of 2M ammonia/methanol. The basic fractions were combined and the solvent removed *in vacuo*. The residue was purified by column chromatography eluting with a gradient of dichloromethane to 5% (2M 0.880 ammonia/methanol)/dichloromethane to afford the title compound; MS (ES+), m/e 344 $[M+H]^+$

Step 3: 4-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-N-3-pyridinylbenzamide



N-3-Pyridinyl-4-(2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)benzamide (product of E245, step 2) (0.031g, 0.090mmol) in dichloromethane (3ml) and glacial acetic acid (0.15ml) was treated with cyclobutanone (0.02ml, 0.18mmol), and 4Å molecoluar sieves (50mg) and stirred at room temperature for 10 minutes. Sodium triacetoxyborohydride (0.038g, 0.18mmol) was added and the mixture stirred for 18 hours at room temperature. The reaction mixture was diluted with methanol and applied to an SCX cartridge (Varian bond-elute) and washed with methanol and then a mixture of 2M ammonia/methanol. The basic fractions were combined and the solvent removed *in vacuo* to afford the title compound; MS (ES+), m/e 398 $[M+H]^+$

Example 246
Phenylmethyl 4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinecarboxylate (E246)

The preparation of E246 is described in Description 4.

Example 247
Phenylmethyl 4-(3-cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperazinecarboxylate (E247)

The preparation of E247 is described in Description 5.

Example 248
3-Cyclopentyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E248)

The preparation of E248 is described in Description 6.

Example 249
3- Cyclobutyl-7-(1-piperazinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E249)

The preparation of E249 is described in Description 7.

Example 250
Phenylmethyl 4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-3,6-dihydro-1(2*H*)-pyridinecarboxylate (E250)

The preparation of E250 is described in Description 11.

Example 251
3-Cyclobutyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E251)

The preparation of E251 is described in Description 12.

Example 252
Methyl 6-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-3-pyridinecarboxylate (E252)

The preparation of E252 is described in Step 3 of Example 198.

Example 253
6-(3-Cyclobutyl-2,3,4,5-tetrahydro-1H-3-benzazepin-7-yl)-3-pyridinecarboxylic acid (E253)

The preparation of E253 is described in Step 4 of Example 198.

Example 254
methyl 5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyrazinecarboxylate (E254)

The preparation of E254 is described in Step 1 of Example 226.

Example 255

5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyrazinecarboxylic acid (E255)

The preparation of E255 is described in Step 2 of Example 226.

Example 256
1,1-dimethylethyl 5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyridinecarboxylate (E256)

The preparation of E256 is described in Step 1 of Example 227.

Example 257
5-[4-(3-cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyridinecarboxylic acid (E257)

The preparation of E257 is described in Step 2 of Example 227.

Example 258
3-Cyclobutyl-7-[1-(5-iodo-2-pyridinyl)-4-piperidinyl]-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E258)

The preparation of E258 is described in Step 1 of Example 228.

Example 259
3-cyclopentyl-7-(4-pyridinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E259)

The preparation of E259 is described in Step 1 of Example 230.

Example 260
3-cyclopentyl-7-(4-piperidinyl)-2,3,4,5-tetrahydro-1*H*-3-benzazepine (E260)

The preparation of E260 is described in Step 2 of Example 230.

Example 261
5-[4-(3-Cyclopentyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-1-piperidinyl]-2-pyrazinecarboxylic acid (E261)

The preparation of E261 is described in Step 1 of Example 233.

Example 262
(5*R*)-3-(3-Cyclobutyl-2,3,4,5-tetrahydro-1*H*-3-benzazepin-7-yl)-5-(hydroxymethyl)-1,3-oxazolidin-2-one (E262)

The preparation of E262 is described in Step 4 of Example 193.

Abbreviations

SCX: Strong cation exchange

Biological Data

A membrane preparation containing histamine H3 receptors may be prepared in accordance with the following procedures:

(i) Generation of histamine H3 cell line

DNA encoding the human histamine H3 gene (Huvar, A. *et al.* (1999) Mol. Pharmacol. **55(6)**, 1101-1107) was cloned into a holding vector, pCDNA3.1 TOPO (InVitrogen) and its cDNA was isolated from this vector by restriction digestion of plasmid DNA with the enzymes BamH1 and Not-1 and ligated into the inducible expression vector pGene (InVitrogen) digested with the same enzymes. The GeneSwitch™ system (a system where in transgene expression is switched off in the absence of an inducer and switched on in the presence of an inducer) was performed as described in US Patent nos: 5,364,791; 5,874,534; and 5,935,934. Ligated DNA was transformed into competent DH5α E. coli host bacterial cells and plated onto Luria Broth (LB) agar containing Zeocin™ (an antibiotic which allows the selection of cells expressing the sh ble gene which is present on pGene and pSwitch) at 50μg ml^{-1}. Colonies containing the re-ligated plasmid were identified by restriction analysis. DNA for transfection into mammalian cells was prepared from 250ml cultures of the host bacterium containing the pGeneH3 plasmid and isolated using a DNA preparation kit (Qiagen Midi-Prep) as per manufacturers guidelines (Qiagen).

CHO K1 cells previously transfected with the pSwitch regulatory plasmid (InVitrogen) were seeded at 2x10e6 cells per T75 flask in Complete Medium, containing Hams F12 (GIBCOBRL, Life Technologies) medium supplemented with 10% v/v dialysed foetal bovine serum, L-glutamine, and hygromycin (100μg ml^{-1}), 24 hours prior to use. Plasmid DNA was transfected into the cells using Lipofectamine plus according to the manufacturers guidelines (InVitrogen). 48 hours post transfection cells were placed into complete medium supplemented with 500μg ml^{-1} Zeocin™.

10-14 days post selection 10nM Mifepristone (InVitrogen), was added to the culture medium to induce the expression of the receptor. 18 hours post induction cells were detached from the flask using ethylenediamine tetra-acetic acid (EDTA; 1:5000; InVitrogen), following several washes with phosphate buffered saline pH 7.4 and resuspended in Sorting Medium containing Minimum Essential Medium (MEM), without phenol red, and supplemented with Earles salts and 3% Foetal Clone II (Hyclone). Approximately 1x 10e7 cells were examined for receptor expression by staining with a rabbit polyclonal antibody, 4a, raised against the N-terminal domain of the histamine H3 receptor, incubated on ice for 60 minutes, followed by two washes in sorting medium. Receptor bound antibody was detected by incubation of the cells for 60 minutes on ice with

a goat anti rabbit antibody, conjugated with Alexa 488 fluorescence marker (Molecular Probes). Following two further washes with Sorting Medium, cells were filtered through a 50μm Filcon™ (BD Biosciences) and then analysed on a FACS Vantage SE Flow Cytometer fitted with an Automatic Cell Deposition Unit. Control cells were non-induced cells treated in a similar manner. Positively stained cells were sorted as single cells into 96-well plates, containing Complete Medium containing 500μg ml^{-1} Zeocin™ and allowed to expand before reanalysis for receptor expression via antibody and ligand binding studies. One clone, 3H3, was selected for membrane preparation.

(ii) Membrane preparation from cultured cells

All steps of the protocol are carried out at 4°C and with pre-cooled reagents. The cell pellet is resuspended in 10 volumes of homogenisation buffer (50mM N-2-hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES), 1mM ethylenediamine tetra-acetic acid (EDTA), pH 7.4 with KOH, supplemented with 10e-6M leupeptin (acetyl-leucyl-leucyl-arginal; Sigma L2884), 25μg/ml bacitracin (Sigma B0125), , 1mM phenylmethylsulfonyl fluoride (PMSF) and 2x10e-6M pepstain A (Sigma)). The cells are then homogenised by 2 x 15 second bursts in a 1 litre glass Waring blender, followed by centrifugation at 500g for 20 minutes. The supernatant is then spun at 48,000g for 30 minutes. The pellet is resuspended in homogenisation buffer (4X the volume of the original cell pellet) by vortexing for 5 seconds, followed by homogenisation in a Dounce homogeniser (10-15 strokes). At this point the preparation is aliquoted into polypropylene tubes and stored at -80°C.

A histamine H1 cell line may be generated in accordance with the following procedure:

(iii) Generation of histamine H1 cell line

The human H1 receptor was cloned using known procedures described in the literature [Biochem. Biophys. Res. Commun. 1994, 201(2), 894]. Chinese hamster ovary cells stably expressing the human H1 receptor were generated according to known procedures described in the literature [Br. J. Pharmacol. 1996, **117**(6), 1071].

Compounds of the invention may be tested for in vitro biological activity in accordance with the following assays:

(I) Histamine H3 functional antagonist assay (method A)

For each compound being assayed, in a solid white 384 well plate, is added:-

(a) 5μl of test compound diluted to the required concentration in 10% DMSO (or 5μl 10% DMSO as a control); and

(b) 30μl bead/membrane/GDP mix prepared by mixing Wheat Germ Agglutinin Polystyrene LeadSeeker® (WGA PS LS) scintillation proximity assay (SPA) beads with membrane (prepared in accordance with the methodology described above) and diluting in

assay buffer (20mM N-2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) + 100mM NaCl + 10mM $MgCl_2$, pH7.4 NaOH) to give a final volume of 30µl which contains 5µg protein and 0.25mg bead per well, incubating at 4°C for 30 minutes on a roller and, just prior to addition to the plate, adding 10µM final concentration of guanosine 5' diphosphate (GDP) (Sigma; diluted in assay buffer).

The plates were then incubated at room temperature for 30 minutes on a shaker followed by addition of:

(c) 15µl 0.38nM [^{35}S]-GTPγS (Amersham; Radioactivity concentration=37MBq/ml; Specific activity=1160Ci/mmol), histamine (at a concentration that results in the final assay concentration of histamine being EC_{80}).

After 2-6 hours, the plate is centrifuged for 5 min at 1500 rpm and counted on a Viewlux counter using a 613/55 filter for 5 min/plate. Data is analysed using a 4-parameter logistical equation. Basal activity used as minimum i.e. histamine not added to well.

(II) Histamine H3 functional antagonist assay (method B)

For each compound being assayed, in a solid white 384 well plate, is added:-

(a) 0.5µl of test compound diluted to the required concentration in DMSO (or 0.5µl DMSO as a control);

(b) 30µl bead/membrane/GDP mix prepared by mixing Wheat Germ Agglutinin Polystyrene LeadSeeker® (WGA PS LS) scintillation proximity assay (SPA) beads with membrane (prepared in accordance with the methodology described above) and diluting in assay buffer (20mM N-2-Hydroxyethylpiperazine-N'-2-ethanesulfonic acid (HEPES) + 100mM NaCl + 10mM $MgCl_2$, pH7.4 NaOH) to give a final volume of 30µl which contains 5µg protein and 0.25mg bead per well, incubating at room temperature for 60 minutes on a roller and, just prior to addition to the plate, adding 10µM final concentration of guanosine 5' diphosphate (GDP) (Sigma; diluted in assay buffer);

(c) 15µl 0.38nM [^{35}S]-GTPγS (Amersham; Radioactivity concentration=37MBq/ml; Specific activity=1160Ci/mmol), histamine (at a concentration that results in the final assay concentration of histamine being EC_{80}).

After 2-6 hours, the plate is centrifuged for 5 min at 1500 rpm and counted on a Viewlux counter using a 613/55 filter for 5 min/plate. Data is analysed using a 4-parameter logistical equation. Basal activity used as minimum i.e. histamine not added to well.

(III) Histamine H1 functional antagonist assay

The histamine H1 cell line was seeded into non-coated black-walled clear bottom 384-well tissue culture plates in alpha minimum essential medium (Gibco /Invitrogen, cat no. 22561-021), supplemented with 10% dialysed foetal calf serum (Gibco/Invitrogen cat no. 12480-021) and 2 mM L-glutamine (Gibco/Invitrogen cat no 25030-024) and maintained overnight at 5% CO_2, 37°C.

Excess medium was removed from each well to leave 10µl. 30µl loading dye (250µM Brilliant Black, 2µM Fluo-4 diluted in Tyrodes buffer + probenecid (145 mM NaCl, 2.5 mM KCl, 10mM HEPES, 10mM D-glucose, 1.2 mM $MgCl_2$, 1.5 mM $CaCl_2$, 2.5 mM probenecid, pH adjusted to 7.40 with NaOH 1.0 M)) was added to each well and the plates were incubated for 60 minutes at 5% CO_2, 37°C.

10µl of test compound, diluted to the required concentration in Tyrodes buffer + probenecid (or 10µl Tyrodes buffer + probenecid as a control) was added to each well and the plate incubated for 30 min at 37°C, 5% CO_2. The plates were then placed into a FLIPR™ (Molecular Devices, UK) to monitor cell fluorescence (λ_{ex}= 488 nm, λ_{EM}= 540 nm) in the manner described in Sullivan *et al.* (In: Lambert DG (ed.), Calcium Signaling Protocols, New Jersey: Humana Press, 1999, 125-136) before and after the addition of 10µl histamine at a concentration that results in the final assay concentration of histamine being EC_{80}.

Functional antagonism is indicated by a suppression of histamine induced increase in fluorescence, as measured by the FLIPR™ system (Molecular Devices). By means of concentration effect curves, functional affinities are determined using standard pharmacological mathematical analysis.

Results

The compounds of Examples E1, E3-9, E11-47, E49-51, E53-56, E58-193, E195-219, E222-231 and E233-245 were tested in the histamine H3 functional antagonist assay (method A). These compounds exhibited antagonism > 6.5 pK_b. More particularly, the compounds of Examples E1, E3, E4, E6-8, E11-18, E29, E43, E81, E87, E91, E96, E98, E100, E105, E108, E111, E115, E120-121, E128, E136, E140-142, E144, E147, E160-161, E165-166, E169, E171, E178, E180, E184, E192, E205-219, E222-229, E233-234, E236-238, E240 and E242-245 exhibited antagonism > 9.0 pK_b.

The compounds of Examples E207, E220 and E221 were tested in the histamine H3 functional antagonist assay (method B). These compounds exhibited antagonism > 8.5 pK_b.

The compounds of Examples E1, E3-9, E11-47, E49-51, E53-97, E102, E105, E107, E110, E115, E120, E129, E131, E134, E142, E155, E191-192, E195, E197-199, E201, E204-231 and E233-245 were tested in the histamine H1 functional antagonist assay and exhibited antagonism < 6.3 pK_b.